

Citation for published version:

Proctor, K, Petrie, B, Lopardo, L, Muñoz, DC, Rice, J, Barden, R, Arnot, T & Kasprzyk-Hordern, B 2021, 'Micropollutant fluxes in urban environment – A catchment perspective', *Journal of Hazardous Materials*, vol. 401, 123745. <https://doi.org/10.1016/j.jhazmat.2020.123745>

DOI:

[10.1016/j.jhazmat.2020.123745](https://doi.org/10.1016/j.jhazmat.2020.123745)

Publication date:

2021

Document Version

Peer reviewed version

[Link to publication](#)

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Journal Pre-proof

Micropollutant fluxes in urban environment – a catchment perspective—Proctor K, Petrie B, Lopardo L, Muñoz DC, Rice J, Barden R, Arnot T, Kasprzyk-Hordern B, Micropollutant fluxes in urban environment – a catchment perspective, *Journal of Hazardous Materials*, doi: 10.1016/j.jhazmat.2020.123745—>



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PII: S0304-3894(20)31734-9

DOI: <https://doi.org/10.1016/j.jhazmat.2020.123745>

Reference: HAZMAT 123745

To appear in: *Journal of Hazardous Materials*

Received Date: 1 March 2020

Revised Date: 6 August 2020

Accepted Date: 15 August 2020

Please cite this article as: { doi: <https://doi.org/>

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Micropollutant fluxes in urban environment – a catchment perspective

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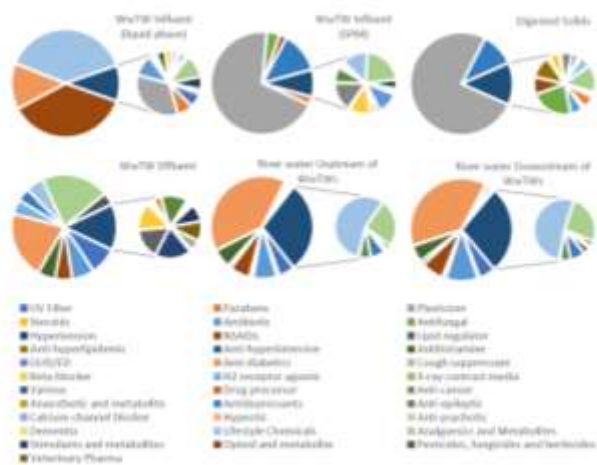
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Graphical abstract



Highlights

- Holistic understanding of the sources and fate of 142 CECs in a river catchment
- 169 kg d⁻¹ of CECs enter WTWs: 168 kg d⁻¹ in the liquid phase, 1.4 kg d⁻¹ in the solid phase
- WTW treatment: 155 kg d⁻¹ removed from the liquid phase across the catchment
- Population normalised loads show low variation in the catchment: 154 ± 12 mg d⁻¹ inh⁻¹
- Direct disposal of unused CECs via sewerage system contributes to localised CEC hotspots

Abstract

This study provided a holistic understanding of the sources, fate and behaviour of 142 compounds of emerging concern (CECs) throughout a river catchment impacted by 5 major urban areas. Of the incoming 169.3 kg d⁻¹ of CECs entering the WwTWs, 167.9 kg d⁻¹ were present in the liquid phase of influent and 1.4

kg d⁻¹ were present in the solid phase (solid particulate matter, SPM). Analysis of SPM was important to determine accurate loads of incoming antidepressants and antifungal compounds, which are primarily found in the solid phase. Furthermore, these classes and the plasticiser, bisphenol A (BPA) were the highest contributors to CEC load in digested solids. Population normalised loads showed little variation across the catchment at 154 ± 12 mg d⁻¹ inhabitant⁻¹ indicating that population size is the main driver of CECs in the studied catchment. Across the catchment 154.6 kg d⁻¹ were removed from the liquid phase during treatment processes. CECs discharged into surface waters from individual WwTWs contributed between 0.19 kg d⁻¹ at WwTW A to 7.3 kg d⁻¹ at WwTW E, which correlated strongly with the respective contributing populations. Spatial and temporal variations of individual CECs and their respective classes were found in WwTW influent (both solid (influent_{SPM}) and liquid phases (influent_{AQ})) throughout the catchment, showing that different urban areas impact the catchment in different ways, with key variables being lifestyle, use of over-the-counter pharmaceuticals and industrial activity. Understanding of both spatial and temporal variation of CECs at the catchment level helped to identify possible instances of direct disposal, as in the case of carbamazepine. Analysis of surface waters throughout the catchment showed increasing mass loads of CECs from upstream of WwTW A to downstream at WwTW D, showing clear individual contributions from WwTWs. Many CECs were ubiquitous throughout the river water in the catchment. Daily loads ranged from 0.005 g d⁻¹ (ketamine, WwTW A) up to 1890.3 g d⁻¹ (metformin, WwTW C) for the 84/138 CECs that were detected downstream of the WwTWs. For metformin this represents the equivalent of ~1,890 tablets (1,000 mg per tablet) dissolved in the river water downstream of WwTW C.

Key words: pharmaceuticals, pesticides, endocrine disruptors, river, wastewater, solids, personal care products, chemicals of emerging concern

1. Introduction

Anthropogenic substances, such as pharmaceuticals, pesticides, plasticizers, UV filters, industrial chemicals etc., have been widely recognised to be entering the environment from a variety of sources. Many of these substances, particularly pharmaceuticals and personal care products ingredients, enter primarily via point sources such as wastewater treatment works (WwTWs), or for other classes such as veterinary pharmaceuticals and pesticides, as diffuse sources such as agriculture.

There are many studies that detail the presence of a range of compounds in a variety of matrices, however the majority of this existing work has been focused on one or two classes at a time, or a small number of compounds of emerging concern (CECs), primarily in aqueous matrices (Boogaerts et al., 2019; Loos et al., 2009; Mole and Brooks, 2019; Musolff et al., 2009; Petrie et al., 2014a). There is a broad range of existing data from a variety of studies (Geissen et al., 2015; Petrie et al., 2014a; Sousa et al., 2018) but due to the large number of potential substances, matrices, methods, and multiple lines of investigation that can be pursued, comparisons between the studies are limited due to the different methods utilised, as they have different quantification parameters. Even the sampling process can have a huge effect on how the results are interpreted, methodological details are often lacking (Ort et al., 2010a; Ort et al., 2010b).

There are fewer studies investigating larger numbers of CECs in solid matrices such as solid particulate matter (SPM), activated and digested sludge, sediments and soils, this may be due to the difficulty of analysing CECs with a variety of different physicochemical parameters in such complicated matrices leading to issues with recoveries and matrix effects with a single extraction method (Petrie et al., 2014a; Proctor et al., 2019). Analysis of solid matrices alongside liquid matrices is critical for a better understanding of the fate and impact of many compounds (Langdon et al., 2012; Petrie et al., 2014a). Some CECs, such as antidepressants, are excreted in or adsorb to SPM before they reach the WwTWs, as well as being released during treatment (Baker and Kasprzyk-Hordern, 2011). The solids produced during WwTW processes, are treated to remove excess water and dangerous pathogens by a variety of processes. This digested sludge, usually termed 'biosolids' is often applied directly to soil as it is rich in nutrients suitable for crops (Kinney et al., 2006; Langdon et al., 2012), but these biosolids have been widely found to be a concentrated source of contaminants. Despite this the CEC content is not widely monitored on a national level nor are the levels of any

of CECs entering the environment in this manner controlled by any legislation, although steps are being put in place to review the current chemicals lists of interest in biosolids in a number of countries (Stutt et al., 2019)..

Despite the limitations of studies discussed above, they clearly show that a single wastewater or environmental sample can or has the potential to contain many different CECs from different classes. Furthermore, many studies have shown the products of metabolism, degradation and transformation of many of these CECs are/have the potential to also be present. Overall this leads to a very complex issue in understanding true exposure levels in the environment and the potential risk they may pose.

Identification of mixtures of co-occurring, high risk CECs, or priority mixtures, is one of the challenges in water quality monitoring (Altenburger et al., 2015). To gain further understanding of these mixtures, their consistency/fluxes within the environment will allow a better understanding of the environmental risk posed by these CECs. Understanding the fluxes of these mixtures will allow the potential changes in risks to be anticipated, potentially leading to optimised treatment and mitigation of risk to the environment. Currently, further work is required to investigate the composition of the mixture in samples from a range of matrices. This will not only require analysis of the mixtures present, but it will provide insight into spatial and temporal trends, between matrices and across a catchment.

The aim of the paper is to investigate the changes in micropollutant load throughout a river catchment system in the South-West of the UK, to gain further information on their sources, fate and behaviour. This was achieved by undertaking a comprehensive investigation of 142 CECs, previously prioritised and analytical method validated (Proctor et al., 2019), at five strategic WwTWs representing >75% of the catchment population. At each WwTW, influent (both liquid and solid phases) and effluent wastewater, digested solids, and upstream and downstream river water were monitored for 7 consecutive days. Five aspects were considered: 1) spatial and temporal variations in the influent, 2) partitioning between aqueous (influent_{AQ}) and solid phases (influent_{SPM}) in the influent, 3)

percentage removal of CECs from the liquid phase, 4) mixture profiles of CECs in all matrices, and 5) spatial trends in river water composition throughout the catchment. This provides a high resolution and more holistic view of the distribution of these CECs throughout the catchment.

2. Materials and methods

2.1. Materials

All materials used in the investigation are detailed in the Supporting information (SI), Section S1. The analytical standards were of the highest purity of $\geq 97\%$, with the exception of azithromycin with 94.2 % and benzophenone-2 with 95.0 % and purchased from Sigma Aldrich, LGC standards or Toronto Research Chemicals (TRC). The solvents used were of HPLC grade. All glassware was silonised to prevent losses of analytes to the untreated glassware. The classes covered by this study are shown in Table 1. Due to the wide range of CECs and complex matrices, not all CECs could be validated for every matrix. Table 1 shows the CECs which are present in each class (green box) and which are validated for each matrix in a previous paper (Proctor et al., 2019).

2.2. Sampling methods and location

Samples were collected at each of the five WwTWs (A-E) for 7 consecutive days between June and October 2015. The five WwTWs utilise a range of treatment technology and receive wastewater from different sized populations (Table 2). Sampling was carried out using volume proportional sampling for influent wastewater, time-proportional for effluent and grab sampling for river water upstream and downstream of the effluent discharge point (sample point distance from discharge point is in Table 2). Digested sludge was collected, via grab sampling, on three consecutive days from WwTW B and WwTW E. Further detail and discussion on the methods and location used can be found in the SI: Section S1, 2.1 and 2.2.

2.3. Sample preparation and analysis

Liquid samples were spiked with internal standards and analytes extracted by solid phase extraction (SPE) using OASIS HLB cartridges before analysis with ultra-performance liquid chromatography coupled with tandem mass spectrometry (UPLC-MS/MS) (Waters). The solid samples were frozen, freeze-dried, homogenised, weighed and spiked with internal standard before undergoing microwave assisted extraction (MAE) followed by SPE with OASIS MCX cartridges. Further detail and discussion on the methods used can be found in the SI, Section S1, 2.3, or in the previously published paper on the validation of the method (Proctor et al., 2019)

2.4. Quality control

To ensure the quality of generated data, spiked quality control samples were analysed for both liquid and solid matrices. All samples were spiked with internal standards to compensate for matrix suppression effects, as well as any losses of analyte during sample preparation. All sample analysis was performed in duplicate.

A further element of quality control was considered with regards to river water sampling. To ensure downstream river waters were completely mixed with effluent, mass balances were estimated for carbamazepine (e.g. Equation 1). Carbamazepine was selected due to its resistance to biological degradation and photodegradation, which is expected to be negligible over the short distances between sampling points (Heberer, 2002). Further discussion of this can be found in the SI, Section S1, 2.2.1 and Section S2 and results can be found in Table 2.

3. Results and discussion

The discussion of results in this paper is primarily in loads, i.e. g d^{-1} , as it allows direct comparison between different matrices and sites. Number of CECs per class (c) and number of samples with measurable concentration in each matrix (n) are discussed for some CECs within the text and can be found for all classes in Table 1. General chemical information and physicochemical parameters of the CECs of interest is gathered in Table S8. Further information is available in the SI.

3.1. Solid-liquid phase distribution of CECs within communal discharges

Overall, 112 of the 138 CECs quantifiable in influent_{AQ} were detected at least once during the study entering the five WwTWs. The majority of micropollutants were found at quantifiable levels in influent_{SPM} (74 of the 96). Many of these chemicals (39) were found in all influent_{AQ} and influent_{SPM} samples their classes ranging from antidepressants, analgesics and their metabolites to illicit stimulants e.g. cocaine and industrial chemicals such as parabens, the plasticiser BPA and the UV filter, benzophenone-1.

The chemical content of each phase of influent is distinctly different (Figure 1 and 2). With lifestyle chemicals, such as caffeine, nicotine and their metabolites, NSAIDs (and acetaminophen) and antidiabetics, predominantly found in the aqueous phase (99.4 %, 99.8 % and 96.2 % of the total load of each chemical present in the aqueous phase, on average across the catchment) and making up the majority of the incoming wastewater. Whilst influent_{SPM}, is primarily made up of the plasticiser, BPA (69.6 %), antidepressants (12.9 %) and antifungals (4.1 %). The latter two of which in particular show high levels of sorption to the solid phase over the aqueous, 36.3 % (including metabolites) and 55.4 % respectively.

Much of the differences between the influent_{AQ} and influent_{SPM}, is of course likely due to the physicochemical characteristics of these compounds such as their log K_{ow} , and water solubility. For example, the NSAIDs: ibuprofen, naproxen and acetaminophen have log K_{ow} values of 3.79, 3.10 and 0.29 respectively and water solubility of 41.1, 145, and 30400 mg L⁻¹ and all are primarily found in influent_{AQ} (0.3%, 0.3% and 0.01% of the total load of each compound). These levels of partitioning are far lower than previously reported by Samaras et al. (Samaras et al., 2013), however similar phase distribution was shown by Petrie et al. for crude wastewater (Petrie et al., 2014b). This may be due to differences between WwTWs sewer retention time, as well as physicochemical properties of the matrix (e.g. pH). Despite these low levels of partitioning, ibuprofen, naproxen and acetaminophen are in the top 20 CEC contributors (16, 12, 11 respectively) to total influent_{SPM} load in this study with daily loads of 8.6, 10.1, 11.8 g d⁻¹ (or 6.0 – 9.1 mg d⁻¹ 1000 inh⁻¹ (ibuprofen), 5.7 – 12.8 mg d⁻¹ 1000 inh⁻¹ (naproxen)

and $4.6 - 13.2 \text{ mg d}^{-1} 1000 \text{ inh}^{-1}$ (acetaminophen) if considering population normalised loads). Within influent_{SPM} these three painkillers show similar loads, however with the influent_{AQ} phase, acetaminophen has a much higher normalised load; $44.8 - 77.0 \text{ g d}^{-1} 1000 \text{ inh}^{-1}$ (18.0 % daily variation across the catchment). Whilst, loads for naproxen and ibuprofen were much lower with $3.1 \pm 0.6 \text{ g d}^{-1} 1,000 \text{ inh}^{-1}$ and $2.7 \pm 0.7 \text{ g d}^{-1} 1,000 \text{ inh}^{-1}$ respectively. These pharmaceuticals are commonly found in the influent_{AQ} of many WwTWs across the globe, due to their high usage and availability without a prescription (Sousa et al., 2018). This is despite low excretion rates due to the extensive metabolism of these NSAIDs (Luo et al., 2014). These results are similar to those found by Mendoza et al., where ibuprofen, naproxen and acetaminophen were found to be the most abundant pharmaceuticals of the study (Mendoza et al., 2015; Paíga et al., 2019). Diclofenac and ketoprofen, which are not so readily available over the counter in the UK, present much lower loads ($131.2 \pm 37.9 \text{ mg d}^{-1} 1,000 \text{ inh}^{-1}$ ($n = 35$) and $8.7 \pm 17.5 \text{ mg d}^{-1} 1,000 \text{ inh}^{-1}$, ($n = 7$) respectively) in influent_{AQ} and less frequently in the case of ketoprofen, which only appears at WwTW E. Despite their worldwide use and abundance, their presence in influent_{SPM} is often overlooked.

As previously mentioned, antidepressants and antifungals are two classes for which a high proportion of the total incoming load can be found within influent_{SPM} (36.3% and 55.4 % respectively). Antidepressants (no. of analytes = 13) contribute 12.9 % to the total influent_{SPM} load and antifungals (no. of analytes = 2) contribute 4.1 % (Figure 2). All antidepressants and metabolites in this study, apart from paroxetine ($3.95 \log K_{ow}$, 35.3 mg L^{-1} water solubility) and duloxetine ($4.68 \log K_{ow}$, 13.0 mg L^{-1}) can be found in influent_{SPM}. With $\log K_{ow}$ of the parent compound ranging from 3.28 (venlafaxine) to 5.29 (sertraline), the percentage of the total load of each compound found in influent_{SPM} is between 2.9 % (venlafaxine) to 67.0 % (sertraline). These results are not unusual and similar data has been obtained from wastewater samples collected in a week long study in the Czech Republic (CR) and over a yearlong study in the UK by Baker et al., (Baker et al., 2012; Baker and Kasprzyk-Hordern, 2013). The presence of antifungals, on the other hand, is primarily due to ketoconazole ($\log K_{ow}$ 4.45). This CEC is primarily found in the influent_{SPM}, with 55.8 % of the load in this phase. This result is comparable to a study by Peng et al. (Peng et al., 2012), who also found ketoconazole primarily in influent_{SPM}. In that study, other azoles were also analysed, such as fluconazole, clotrimazole, miconazole, and econazole, all of which

were found in influent_{SPM} only and not influent_{AQ}, showing that this may be a key matrix to investigate for this class and a wider range of antifungals should be considered in future.

Overall lifestyle chemicals, have the highest contribution to this catchment with 38.6% of the load, furthermore the daily variation of this load, normalised by population for these compounds, over the seven days of sampling at each of the five sites ($n = 35$), shows caffeine has one of the lowest daily load variations (23.1 %) of most compounds in this study. The other lifestyle chemicals show more variation; 1,7-dimethylxanthine (26.5 %), nicotine (42.5 %) and its metabolite cotinine (26.2 %) and creatinine (52.1 %). This can provide some insight into the patterns of people's lifestyle habits across a catchment. As an example, wastewater-based epidemiology was applied to caffeine and its metabolite 1,7-dimethylxanthine (methodological details can be found in the SI, Section S3, 1.2.1) to understand usage patterns across the catchment. Overall it was found the loads present suggest an intake of 26 – 57 mg of caffeine per person per day, which is in line with a cup of coffee of a few cups or black tea per day (de Mejia and Ramirez-Mares, 2014; Wishart et al., 2018).

The loads calculated in influent_{SPM} represent a large proportion of antidepressants and antifungals but also for other individual compounds; the anti-cancer drug imatinib (39.9 % partitioning to influent_{SPM}) and the anti-psychotic risperidone (87.7 % partitioning to influent_{SPM}). For some CECs, such as verapamil, thiamethoxam, oxadiazon, methiocarb and donepezil, influent_{SPM} represents all of the total load for these compounds and is therefore the primary route of entry of these CECs to the environment, which may have gone undetected in studies which focus only on the influent_{AQ}. SPM matrix is therefore key to understanding the fate of these classes and CECs.

Various factors are considered important in the consideration of partitioning between liquid and solid phases, these include, water solubility, log K_{ow} , partition coefficient (K_d), log D_{ow} , as well as a compounds polarity and structure. It has been reported before, the likelihood of a compound to sorb to the solid phase increases with log K_{ow} (Hyland et al., 2012). In this study, when considering the classes individually, there is some correlation between these factors, however,

considering the full range of CECs the simplistic model of ‘the higher the log K_{ow} , the more partitioning to solids’ cannot be easily applied. Further work is needed to understand this behaviour.

3.2. Spatial and temporal CEC trends in WwTWs

3.2.1. Overall spatial and temporal trends of CEC loads

The spatial and temporal trends (Figure 1 and 2) of the overall load, in both influent_{AQ} and influent_{SPM}, shows that similar chemical speciation between these two matrices is observed across all WwTWs within this catchment, with the loads in influent_{AQ} being primarily driven by population size (Table S3 and Figure 1). The five WwTWs ranged in size from 18,274 to 867,244 population equivalents. The incoming flow ratio of residential population to commercial/trade also varied from site to site, which is displayed as a percentage of the total population equivalents in Table 2. However, influent_{SPM}, (Table S4 and Figure 2) shows there is far more temporal and spatial variation than appears in the influent_{AQ}.

3.2.1.1. Industrial chemicals

Figure 1 shows a correlation can be seen between higher industrial contributions to wastewater seen at WwTW B (30.0%) and E (23.9%), the total weekly load of BPA, UV filters and parabens and particularly the weekly influent_{SPM} load e.g. 92.8 g week⁻¹ (B) to 6522 g week⁻¹ (E) (BPA), 2.9 g week⁻¹ (B) to 10.3 g week⁻¹ (E) (UV filters), and 14.8 g week⁻¹ (B) to 218.5 g week⁻¹ (E) (parabens) compared with 7.5 g week⁻¹ (D) to 23.6 g week⁻¹ (C), 0.1 g week⁻¹ (D) to 0.6 g week⁻¹ (C), 1.2 g week⁻¹ (D) to 5.0 g week⁻¹ (C) respectively at the other WwTWs. This can also be seen in the population normalised loads (Figure 1 and 2), although the correlation is far clearer in the influent_{SPM}, than the influent_{AQ}. BPA, in particular, contributes 45.4 % (WwTW B) to 72.8 % (WwTW E) to the total load of influent_{SPM} throughout the campaign. This equates to total population equivalent normalised loads of 29.5 – 694.3 mg d⁻¹ 1,000 inh⁻¹ and 40.6 – 2827 mg d⁻¹ 1,000 inh⁻¹ for WwTWs B and E, respectively. When comparing these results to the 7.0 %, 10.8 % and 16.8 % (partitioning to influent_{SPM}) or 6.7 mg d⁻¹ 1,000

inh⁻¹ (minimum at C) to 307.2 mg d⁻¹ 1,000 inh⁻¹ (maximum at D), it is a considerable portion. Furthermore, clear temporal trends can also be seen for BPA in both phases (Figure S3), showing increasing levels throughout the working week, reducing to lower levels over the weekend. The presence of BPA in domestic wastewater has previously been linked to leaching from plastics, such as pipes or drinking bottles which would account for the low level loads commonly seen (Flint et al., 2012; Petrie et al., 2019; Rubin, 2011). The increase levels from industrial waste may be linked to the production of epoxy resins, polycarbonate plastics and thermoprinting paper, however it has not been linked to a specific trade within this catchment at this time. The presence and trends of this compound in this catchment is described in more detail by Petrie et al. and Lopardo et al. (Lopardo et al., 2019; Petrie et al., 2019).

The personal care product ingredient methylparaben, also shows specific industrial spatial and temporal trends. It is present at a constant level across the week at WwTWs A, C and D, with normalised loads in influent_{AQ} ranging from 564.6 – 976.1 mg d⁻¹ 1,000 inh⁻¹. It is often found in personal care products such as shampoos and shower gels. Therefore, for this CEC, a consistent level across the week is expected. However, at WwTWs with higher industrial input e.g. WwTW B and E, the trends seen in influent_{AQ} show significant increase of methylparaben on certain days of the week, which may be as a result of relevant industrial processes, such as toiletry manufacture, which is known to be present in the area. These trends can be seen in both influent_{AQ} and influent_{SPM} (FigureS3), as levels increase from across the working week and decrease over the weekend (up to 16,242 mg d⁻¹ 1000 inh⁻¹ on Thursday to 681.0 mg d⁻¹ 1,000 inh⁻¹ on Sunday in influent_{AQ} and up to 48.2 mg d⁻¹ 1,000 inh⁻¹ on Thursday to 8.5 mg d⁻¹ 1,000 inh⁻¹ on Sunday in influent_{SPM} at WwTW B, whereas for WwTW E the trends are strongest in the influent_{SPM} with trends increasing up to 41.9 mg d⁻¹ 1,000 inh⁻¹ on Friday to 15.5 mg d⁻¹ 1,000 inh⁻¹ on Sunday). The influence of industrial activity on the highly variable loads of these chemicals, may have a significant environmental impact, if they are not effectively removed.

3.2.1.2. Illicit drugs

Spatial trends were also observed for some illicit stimulants, demonstrating variation in the usage behaviour throughout the catchment area. It was postulated that those areas with the greater population size and night life (WwTWs C and E) would see the greater loads of illicit stimulants (e.g. MDMA, cocaine, amphetamine and mephedrone) due to recreational usage. Cocaine, amphetamine and MDMA followed this trend. For example, at WwTWs C and E, total MDMA loads (sum of both $\text{influent}_{\text{AQ}}$ and $\text{influent}_{\text{SPM}}$) were found up to 120.8 and 157.1 $\text{mg d}^{-1} 1,000 \text{ inh}^{-1}$ respectively (Tables S3 and S4). At the remaining sites, maximum loads were found in the range 33.3 – 79.9 $\text{mg d}^{-1} 1,000 \text{ inh}^{-1}$. Previous studies have found cocaine, amphetamine and MDMA use to be greater in large urban populations than in smaller more rural locations (Lai et al., 2016; Nefau et al., 2013). In contrast, mephedrone loads were highest at WwTW D which treats wastewater from the smallest population size (18,274 inhabitants). Total influent loads ranged between 13.1 and 38.9 $\text{mg d}^{-1} 1,000 \text{ inh}^{-1}$ in comparison to loads of 3.8 to 8.5 $\text{mg d}^{-1} 1,000 \text{ inh}^{-1}$ at WwTW C and 7.2 to 20.5 $\text{mg d}^{-1} 1,000 \text{ inh}^{-1}$ at WwTW E (Table S3 and S4). Mephedrone was not detected in wastewater at WwTWs A and B.

The weekly trends for stimulants are also very pronounced (Figure S2). There was an increasing weekend load of not only MDMA and cocaine but also their metabolites: MDA (MDMA), benzoylecgonine (cocaine) and cocaethylene (combination of cocaine and alcohol), but not anhydroecgonine methylester (metabolite from smoking crack cocaine). This shows increased usage of both MDMA and cocaine throughout the catchment during the weekend, though this is less pronounced in areas that are less populated, more rural and with less night life. These trends have previously been seen on numerous occasions across the world (US, (Gushgari et al., 2018), Czech Republic (Baker et al., 2012), England and Europe (Castrignanò et al., 2018b), China (Zhang et al., 2019). The trends, shown in Figure S3, can also be seen in $\text{influent}_{\text{SPM}}$ for both cocaine, benzoylecgonine and MDMA, despite there being proportionately less load present in $\text{influent}_{\text{SPM}}$, 1.4 %, 0.1 %, and 0.9 % respectively. Interestingly, a spike in load is observed on one day for $\text{influent}_{\text{SPM}}$, rather than over the entire weekend for $\text{influent}_{\text{AQ}}$.

3.2.1.3. Pharmaceuticals linked to hospital effluent

Total population normalised loads of the analgesic morphine were greater at WwTWs C and E. With ranges between 377.5 to 607.6 mg d⁻¹ 1,000 inh⁻¹ at WwTW C and 372.2 to 443.1 mg d⁻¹ 1,000 inh⁻¹ at WwTW E, compared to the other sites which ranged between 184.5 mg d⁻¹ 1,000 inh⁻¹ at WwTW A to 284.9 mg d⁻¹ 1,000 inh⁻¹, also at WwTW A (the ranges of the remaining two WwTWs are quite similar and fall within this range (Tables S3 and S4). Higher morphine loads at WwTWs C and E can be attributed to hospitals within their catchment areas, similar to a study conducted in Portugal, which found that 51 % of the total analgesic load in municipal wastewater was from hospitals (Santos et al., 2013). However, within this catchment a more detailed investigation is required to confirm the contribution of hospital wastewater. Furthermore, the anti-cancer drug ifosfamide was only detected in wastewater at WwTWs C and E (Table S3 and Table S4). Although ifosfamide is not directly linked to hospital wastewater, as it can be excreted from the homes of patients receiving chemotherapy, it was not detected at WwTWs which did not receive hospital wastewater.

3.2.1.4. Lifestyle chemicals and pharmaceuticals

Many CECs, such as lifestyle chemicals and some NSAIDs, which are freely available without prescription and used widely, show little variation between sites across the catchment e.g. caffeine, with average loads of $23,826 \pm 5,498$ mg d⁻¹ 1,000 inh⁻¹, showing 23.1% daily variation across the catchment, acetaminophen, with $58,374 \pm 10,494$ mg d⁻¹ 1,000 inh⁻¹ and 18.0%, and ibuprofen with $3,092 \pm 629$ mg d⁻¹ 1,000 inh⁻¹ and 20.4%.

This trend continues with many pharmaceuticals which are prescribed widely for chronic conditions e.g. the anti-diabetic, metformin, (daily variation across the catchment = 21.5 %, with average total influent load of $20,260 \pm 4,357$ mg d⁻¹ 1,000 inh⁻¹), analgesic for moderate pain, tramadol, (17.4 %, 241.3 ± 42.1 mg d⁻¹ 1,000 inh⁻¹), and the antidepressants, citalopram (14.5 %, 108.0 ± 15.6 mg d⁻¹ 1,000 inh⁻¹) and amitriptyline (20.5 %, 53.9 ± 11.1 mg d⁻¹ 1,000 inh⁻¹). Interestingly, compounds in the same class, which appear at much lower loads, show more spatial variation and minimal temporal variation e.g. the anti-diabetic, sitagliptin (35.7 %, 70.2 ± 25.0 mg d⁻¹ 1,000 inh⁻¹), and the antidepressant, fluoxetine (41.0 %, 20.7 ± 8.5 mg d⁻¹ 1,000 inh⁻¹). This may be a sign of variation in prescribing

behaviour of healthcare professionals (Rowlingson et al., 2013), spatial variation in the prevalence of relevant conditions, or it may be due to differences in the stability of the pharmaceutical within the sewer and the difference in sewer residence time to the site. This has been found to be an issue with illicit drug monitoring and other pharmaceuticals have shown the potential to degrade within sewers (Gao et al., 2017; Jelic et al., 2015; McCall et al., 2016). Further investigation is required to provide a more detailed assessment.

Antibiotics and antibacterial compounds ($c = 19$), only contribute a small proportion, 1.1 %, to the total influent_{AQ} load, and influent_{SPM} load, 1.0% ($c = 7$). Several of these CECs, such as sulfasalazine, clarithromycin, azithromycin, trimethoprim, sulfamethoxazole and triclosan were found in all influent_{AQ} samples at all WwTWs (with the exception of azithromycin, which was missing from one sample at WwTW A), but showed highly variable population normalised loads (Table S3). Within influent_{SPM}, only trimethoprim was found in all samples, ranging from $1.4 \text{ mg d}^{-1} 1,000 \text{ inh}^{-1}$ at WwTW B to $13.7 \text{ mg d}^{-1} 1,000 \text{ inh}^{-1}$ at WwTW C. Few other antibiotics were found in SPM, only sulfadiazine was found with some regularity and only at WwTW B (100% of samples at population normalised loads between 0.9 to $2.2 \text{ mg d}^{-1} 1,000 \text{ inh}^{-1}$). Unfortunately, this method was unable to quantify fluoroquinolones in this matrix, a class of antibiotics known for their ability to partition to the solid phase (Castrignanò et al., 2018a; Martín et al., 2015; Petrie et al., 2014b), therefore the antibiotic load of this matrix is likely to be underestimated for these compounds. Despite this it is clear that these compounds are widely used (from influent_{AQ} results) and two, azithromycin and clarithromycin, have been placed on the WFD Watch List as substances of potential environmental concern (Carvalho et al., 2015).

Ciprofloxacin and erythromycin are also present on this list and yet within this catchment they are detected less frequently within the influent_{AQ} ($n = 7$ and 21), though their loads, when found, are significant (ciprofloxacin $15.8 \pm 10.6 \text{ g d}^{-1}$ at WwTW A only, and erythromycin is found at levels between $9.0 \pm 1.9 \text{ g d}^{-1}$ at WwTW D to $189.6 \pm 13.6 \text{ g d}^{-1}$ at WwTW E). Other antibiotics, such as metronidazole, sulfadiazine, cefalexin, ofloxacin, tetracycline, danofloxacin, and chloramphenicol are found sporadically in the influent_{AQ} throughout the catchment, often at lower loads than the other antibiotics. Their sporadic presence may be due to limited use. Further consideration of prescription levels will provide a clearer understanding, but this is outside the scope of this paper.

Trends of the population normalised loads for antibiotic and antibacterial compounds show some variation between WwTWs and between individual compounds. For example, WwTW B shows the highest population normalised loads for sulfasalazine ($93.1 \pm 28.5 \text{ mg d}^{-1} 1,000 \text{ inh}^{-1}$ compared to $45.0 \pm 15.1 \text{ mg d}^{-1} 1,000 \text{ inh}^{-1}$ at WwTW A which has the lowest), azithromycin ($135.7 \pm 70.4 \text{ mg d}^{-1} 1,000 \text{ inh}^{-1}$ compared to $21.9 \pm 15.5 \text{ mg d}^{-1} 1,000 \text{ inh}^{-1}$ at the lowest at WwTW A), and triclosan ($405.5 \pm 181.1 \text{ mg d}^{-1} 1,000 \text{ inh}^{-1}$ compared to $154.1 \pm 10.2 \text{ mg d}^{-1} 1,000 \text{ inh}^{-1}$ at the lowest at WwTW C). However, WwTW B also has the lowest levels for other antibiotics such as clarithromycin ($209.8 \pm 49.4 \text{ mg d}^{-1} 1,000 \text{ inh}^{-1}$ compared to $369 \pm 86.6 \text{ mg d}^{-1} 1,000 \text{ inh}^{-1}$ at WwTW D), trimethoprim ($99.0 \pm 7.8 \text{ mg d}^{-1} 1,000 \text{ inh}^{-1}$ compared to $247.1 \pm 21.5 \text{ mg d}^{-1} 1,000 \text{ inh}^{-1}$ at WwTW C), and the second lowest for sulfamethoxazole levels at $18.8 \pm 6.7 \text{ mg d}^{-1} 1,000 \text{ inh}^{-1}$, which is less than 20 % of the highest levels ($100.5 \pm 6.6 \text{ mg d}^{-1} 1,000 \text{ inh}^{-1}$ WwTW E). This variation may be due to differences in the prescription practices, which could be influenced by variable uptake of prescription advice from the Government as part of the UK Five Year Antimicrobial Resistance Strategy (Department of Health & and Department for Environment Food and Rural Affairs United Kingdom, 2013).

Some CECs, particularly pharmaceuticals, that are regularly and widely used by the population, show no temporal trends throughout the week. This is to be expected, as those pharmaceuticals that are sporadically but widely used, such as NSAIDs and painkillers e.g. acetaminophen and ibuprofen (Figure S2), will show only small variations in load. Other pharmaceuticals, such as antibiotics, are used in treating specific conditions and often require courses of several days, but may be prescribed less often, so are used less widely. Antibiotics, such as sulfamethoxazole and trimethoprim which are often prescribed together (as co-trimoxazole) as a long administration course (14 - 21 days), show a steady trend across the week. Other antibiotics, with typically shorter courses, such as azithromycin, clarithromycin, metronidazole and ciprofloxacin, show more variation across the week. To see trends of these compounds, longer term studies are required to cover time periods encompassing seasons or even years, such as those performed in CR, Greece, Spain, and New Zealand (Golovko et al., 2014; Kumar et al., 2019; Mastroianni et al., 2017; Papageorgiou et al., 2016). This would be particularly useful for antibiotics as it will indicate whether reducing

prescription reduces the influent load and any seasonal trends may indicate incorrect prescribing practices (from prescriptions of antibiotics for flu during winter months for which it is not effective) (Coutu et al., 2013; Golovko et al., 2014).

3.2.1.5. Veterinary pharmaceuticals and pesticides

Surprisingly, the veterinary antibiotic, sulfapyridine, is present at population normalised loads, for total influent, ranging from $205.4 \pm 23.8 \text{ mg d}^{-1} \text{ inh}^{-1}$ to $299.8 \pm 25.8 \text{ mg d}^{-1} \text{ inh}^{-1}$ and shows little daily variation (17.8 %) across the sampling campaign. It has been found previously at low level in influent_{AQ} and its presence has been linked to human use (Ebele et al., 2017; Golovko et al., 2014; Paíga et al., 2016; Wilkinson et al., 2017) as well as veterinary use (Sarmah et al., 2006). However, this antibiotic is no longer prescribed or advised for use by humans in the UK, as it is of critical importance for use with food producing animals, but it is also produced during the human metabolism of sulfasalazine (European Medicines Agency, 2019; Kasprzyk-Hordern et al., 2008; Peppercorn, 1984; Wishart et al., 2018). In this study, it is thought this metabolism of sulfasalazine may be the main source contributing to sulfapyridine's consistent presence across the catchment. This can also be seen in the similarity of their temporal and spatial trends. It is thought that if the main contributing factor was due to usage on livestock, its presence would not be consistent across the catchment, as large variances between rural areas (WwTW B) and highly urban areas (WwTW E) would be expected. Furthermore, the similarity in temporal and spatial trends with sulfasalazine would be very unlikely. Sarafloxacin and diazinon were the only other veterinary pharmaceuticals found, with sarafloxacin only found at in one influent_{AQ} sample at WwTW D at $5.7 \text{ mg d}^{-1} 1000 \text{ inh}^{-1}$ and diazinon found across the catchment in 80% of the influent_{AQ} samples and 22.9% of the influent_{SPM} samples at total influent loads ranging from $0.6 \text{ mg d}^{-1} 1000 \text{ inh}^{-1}$ (WwTW C) to $85.5 \text{ mg d}^{-1} 1000 \text{ inh}^{-1}$ (WwTW E). Interestingly, diazinon is primarily found in influent from the larger WwTWs serving the two major cities. This is it perhaps an indication of a larger numbers of pets relative to inhabitants in these areas compared to more rural areas, or a higher prevalence in the use of deworming medication for which it is primarily used. Overall, veterinary pharmaceuticals and pesticides represent a small proportion, < 0.5% of the total influent chemical load, of the CECs analysed.

3.2.1.6. Anticipated and accidental micropollutant fluxes

Considering the temporal and spatial distribution of CECs across the catchment allows a better understanding over the micropollutant mixtures and fluxes of load that are experienced by the WwTWs, allowing for pattern to emerge regarding human behaviour, degradation and seasonal changes in larger studies. This will allow the loads and fluxes to be anticipated allowing optimisation of treatment technologies for better removal of these contaminants. However, studying the trends in this work anomalies can be detected.

Figure 2 shows a significantly higher proportion of the total load of influent_{SPM} is due to antifungals, specifically ketoconazole, as griseofulvin was not found at this site. Ketoconazole was found in all influent_{SPM} samples at all sites, showing its frequent and widespread use. At WwTW C however, the normalised loads were on average $79.2 \pm 35.7 \text{ mg d}^{-1} 1,000 \text{ inh}^{-1}$ compared to the 27.5 to $50.2 \text{ mg d}^{-1} 1,000 \text{ inh}^{-1}$ at the other sites. The high standard deviation seen at WwTW C compared to the other sites may be more indicative of incorrect usage, incidental release or direct disposal rather than difference in prescription.

A similar situation is seen at WwTW A, as anti-epileptics represent a far higher proportion of influent_{SPM} (25.4 %, Figure 2). This is entirely due to the presence of the parent compound as the metabolite 10,11-dihydro-10-hydroxycarbamazepine was not detected in influent_{SPM} and the other metabolite, carbamazepine-10,11-epoxide could not be analysed in influent_{SPM}. The normalised loads of carbamazepine at WwTWs B-E were in the range of <MQL (1 sample at WwTW D) to $5.3 \pm 8.0 \text{ mg d}^{-1} 1,000 \text{ inh}^{-1}$, whilst at WwTW A they were $119.3 \pm 287.4 \text{ mg d}^{-1} 1,000 \text{ inh}^{-1}$. This standard deviation indicates a very skewed distribution of carbamazepine load at WwTW A, which is not consistent for a pharmaceutical used solely to treat chronic conditions. This is likely a further example of incorrect usage or direct disposal of unused carbamazepine. To gain further understanding of this distribution, the temporal trends were considered.

For ketoconazole, with a normalised load of $79.2 \pm 35.7 \text{ mg d}^{-1} 1,000 \text{ inh}^{-1}$ at WwTW C, it shows high daily variation through the week (45.0%) with high loads seen on Monday-Wednesday and lower throughout the rest of the week. A similar trend is also seen at WwTW B with the highest loads on Tuesday and Wednesday and a daily variation of 44.1 %, the other sites have daily variation of 21.5 – 29.7 %. From further research, this is likely due to the primary mode of administration of this pharmaceutical in the form of a medicated shampoo (based on prescription data from this catchment), which is applied one to two times a week for the prevention or treatment of seborrheic dermatitis and dandruff (20 mg g^{-1}) and is available both over the counter and with a prescription (National Health Service Business Services Authority, 2019; Wishart et al., 2018).

Carbamazepine shows a significant increase in influent_{SPM} load on Sunday at WwTW A, which is not seen in the metabolites. In influent_{AQ}, the carbamazepine load increases by >300 %, from the average load of 4.3 g d^{-1} to 12.7 g d^{-1} . Carbamazepine has previously shown no measurable degradation under typical sewer conditions (O'Brien et al., 2017), therefore the levels seen are likely unchanged from entering the sewer. Within the catchment of this WwTW, this pharmaceutical is mainly administered in tablet form as 100, 200, or 400 mg (National Health Service Business Services Authority, 2019; Wishart et al., 2018). Therefore, this peak represents disposal of between $21 \times 400 \text{ mg}$ tablets or $84 \times 100 \text{ mg}$ tablets. In influent_{SPM}, the same trend can be seen, however it occurs to a greater magnitude (from the mean of the rest of the week: 0.2 g d^{-1} to 30.2 g d^{-1} on Sunday). When influent_{SPM} is combined with influent to calculate a total load, the increase is from 4.5 g d^{-1} to 42.9 g d^{-1} , which suggests disposal between $96 \times 400 \text{ mg}$ tablets or $384 \times 100 \text{ mg}$ tablets. The percentage partitioning for this day was drastically altered from the 3.6 % average for the remainder of the week to the high value to 70 % on the day. This is perhaps indicative of the disposal of a highly concentrated solid load.

Fluoxetine disposal has been previously observed within this catchment, which was attributed to ~915 pills, as described by Petrie et al. (Petrie et al., 2016), adding to evidence which suggests direct disposal of pharmaceuticals is more common than previously thought. Within that study Petrie et al. proposed a

framework to differentiate between normal, daily usage of these CECs and direct disposal of them in influent. It is likely that the use of 24-hour composites with a short period between subsample collection allowed these events to be captured. Currently, the effects of these unexpected spikes of CECs are unknown. The biological treatments at WwTWs will largely adapt to the everyday fluxes of CEC load, however, the sudden increase in CECs such as carbamazepine, ketoconazole or fluoxetine could potentially cause changes in the microbiology that reduce treatment efficiency. Furthermore, these events will likely lead to an increase in load and concentration leaving the works, which may cause a similar phenomenon with the environmental flora and fauna, as it is exposed to an acute impact of CEC load.

3.2.2. CEC removal from the liquid phase during WwTW treatment

The catchment-scale study enabled the performance of five WwTWs for the removal of micropollutants to be assessed under similar weather conditions (Table S9). Percentage removal (% removal) was calculated as described in Section S2, SI. To summarise, it is the percentage reduction in load of a CEC between liquid phases of influent (influent_{AQ}) and effluent. The process types monitored include two activated sludge treatments, conventional activated sludge (CAS) (WwTWs A and E), and sequencing batch reactors (SBRs) (WwTW E). Trickling (rotating biological) filters (TF) configured with different bed media were used at the remaining WwTWs (WwTW B, C and D). CAS is generally considered to achieve greater micropollutant removals than TFs from collated full-scale data (Baker and Kasprzyk-Hordern, 2013; Kasprzyk-Hordern et al., 2009). This is considered to be as a result of longer hydraulic retention times (HRT) associated with CAS, enabling greater contact time for biodegradation. HRTs for this catchment can be found in Table 2. However, this study found this is not the case for all classes of CECs. Figure S1 shows average percentage removals \pm relative standard deviation per site and overall removal in bar charts, the data for which can be found in Table S7. Figure 6 shows the removal data of selected classes of CECs across all WwTWs in the form of box plots.

The removal of lifestyle chemicals and creatinine were high, with creatinine removed at 99.6 ± 0.9 %, caffeine at 97.8 ± 1.8 %, nicotine at 96.6 ± 3.1 %, 1,7-dimethylxanthine at 95.6 ± 3.6 % and cotinine at 93.2 ± 5.7 %. The CAS and SBR WwTWs (WwTWs A, E) show better removals for caffeine and nicotine and significantly better removals for their metabolites. This is in line with removals seen at other sites in the UK with TFs and CAS in a study by Baker et al (Baker and Kasprzyk-Hordern, 2013).

This trend can be seen in the NSAIDs, where this pattern continues with acetaminophen (only slight improvement at WwTWs A, E due to such high removal 99.4 ± 0.7 %), ibuprofen (94.4 ± 5.3 %), and naproxen (83.0 ± 12.9 %). In contrast, diclofenac shows the best removal at sites with TFs (WwTWs B-D, removal range 29.0 – 64.5 %), and worst at WwTW E (-3.0 ± 10.7 %). Ketoprofen showed 11.4 ± 9.9 % removal at WwTW E but was not detected at the other sites and therefore removal cannot be determined. The trend seen for the other NSAIDs is consistent with those found by Martín et al. and Kasprzyk-Hordern et al., (Kasprzyk-Hordern et al., 2009; Martín et al., 2012).

The plasticiser, BPA (93.0 ± 3.6 %), and other industrial and personal care product ingredients, generally show high removal across the catchment with little variation between sites, such as the UV filters (benzophenone-1 with 96.6 ± 3.1 %, benzophenone-2 with 99.6 ± 0.8 %, benzophenone-3 with 91.7 ± 2.0 %, not benzophenone-4 with 32.6 ± 32.3 % removal however), and all parabens (methylparaben with 99.5 ± 0.3 %, ethylparaben with 99.8 ± 0.4 %, propylparaben with 99.2 ± 0.7 % and butylparaben with 100.0 ± 0.0 % removal). This is consistent with removals obtained for these CECs at sites with TFs and CAS treatment in Wales (Kasprzyk-Hordern et al., 2009).

Several antidepressants show low-medium level removal with little variation between TF WwTWs B-D, i.e. citalopram (average removals are between 17.3 to 20.5 %), amitriptyline (50.9 to 57.6 %) and sertraline (53.1 to 58.2 %), but show the medium to high levels of removal at CAS WwTW A (51.5 ± 19.4 %, 87.6 ± 10.2 %, and 54.4 ± 24.1 % for citalopram, amitriptyline and sertraline respectively). Kasprzyk-Hordern et al., found similar levels of removal for amitriptyline at

both TFs and CAS sites (Kasprzyk-Hordern et al., 2009). Mirtazapine shows similar levels of removal for WwTWs A-C (22.0 ± 6.3 %) and had the highest levels of removal at WwTW D (39.8 ± 11.4 %). Venlafaxine saw negative removals at WwTWs A-C (-28.8 ± 14.5 %) and, similarly to mirtazapine, showed the highest levels of removal at WwTW D, 28.4 ± 23.6 %. Fluoxetine also shows negative removal at WwTW A-B (-53.8 to -27.4 %), WwTW C showed high highest levels of removal 32.7 ± 8.9 %, no overall removal at WwTW D. Both venlafaxine and fluoxetine have previously shown greater removal levels at both TF and CAS sites (Baker and Kasprzyk-Hordern, 2013; Verlicchi et al., 2012). WwTW E showed the worst removals for all antidepressants, ranging from -81.3 % for fluoxetine to 35.7 % for sertraline (except venlafaxine, which showed negligible removal at this site), this may be due to the short hydraulic residence time (HRT = 10.9 h) in the main treatment stream (90 % sequencing batch reactors) at this site. The antidepressant metabolites were either completely removed (norfluoxetine, nortriptyline), similar to results found by Baker et al., and Comber et al., (Baker and Kasprzyk-Hordern, 2013; Comber et al., 2019), were removed similarly to the parent drug (desmethylcitalopram), or increased in load between influent_{AQ} and effluent, likely due to degradation of the parent drug into the metabolite (nortriptyline, desmethylvenlafaxine), similar to what was found by Baker et al. and Paíga et al., (concentration based calculation of removal, rather than load) (Baker and Kasprzyk-Hordern, 2013; Paíga et al., 2019).

Carbamazepine and its metabolites, carbamazepine-10,11-epoxide and 10,11-dihydro-10-hydroxycarbamazepine, show increased levels between influent_{AQ} and effluent at the CAS WwTW A. 10,11-dihydro-10-hydroxycarbamazepine forms O-glucuronides during human metabolism, which can be cleaved by β -glucuronidase, from faecal bacteria, leading to this increase (Ta et al., 1999). Carbamazepine and carbamazepine-10,11-epoxide, on the other hand, form N-glucuronides during human metabolism, which have shown they cannot be degraded by this enzyme but still show increased loads in effluent (Bahlmann et al., 2014).

The lack of degradation for tramadol in this study contrasts with the results found by Baker et al., for both TFs and CAS, however, it is comparable to removal levels found by Kasprzyk-Hordern et al., and Archer et al., (Archer et al., 2017; Baker and Kasprzyk-Hordern, 2013; Kasprzyk-Hordern et al., 2009). The O-desmethyltramadol metabolite can be further metabolised to form O-glucuronides (Wishart et al., 2018), which as previously discussed, are cleaved during biological treatment.

The high removal of the lifestyle chemicals, NSAIDs, parabens and plasticisers has led to a very different profile for treated wastewater compared to raw wastewater. This is observed in analgesics and metabolites, which represent a quarter of the total load after treatment. Anti-diabetics also show an increased proportion of the total load, due to relatively low removal at the WwTWs. Overall, antibiotics are poorly removed, < 50 %, although WwTWs A and E have higher levels of removal for sulfasalazine (73.7 ± 9.2 % WwTW A and 71.8 ± 3.2 % at WwTW E) and clarithromycin (83.0 ± 9.8 % WwTW A and 64.3 ± 7.3 % WwTW E). WwTW E removed 74.2 ± 7.3 % and 68.7 ± 6.1 % of azithromycin and sulfamethoxazole respectively, but A has very poor removal for these compounds. WwTWs using biological activated sludge have previously shown reasonable removal for these compounds, similar to what was seen at WwTW E in this study (Golovko et al., 2014). Furthermore, it shows that long term seasonal changes may have further effects on removal that are not seen in this study, but which should be taken into account for the wider picture.

In summary, although, previously CAS was considered a better micropollutant removal process than TFs, this considered a smaller range of compounds (Baker and Kasprzyk-Hordern, 2013; Kasprzyk-Hordern et al., 2009). The larger range of compounds considered in this study shows this is not so clear cut and there is great variation between classes, as well as CECs within the classes. In the next section overall mass balance is taken into consideration and may provide a clearer result.

3.2.3. CEC mass balance in studied WwTWs

The estimated total mass of 119 of the 138 CECs in this work entering (quantifiable in total influent) the WwTW of this catchment is 1,185 kg per week (wk^{-1}) (or 1,847 kg wk^{-1} with creatinine). Influent_{SPM} contributes only 0.8 % (9.6 kg wk^{-1}) of the total load, but as seen in Figures 1 and 2, it has a very different chemical profile. This results in total mass loads of 135 to 167 g d^{-1} 1,000 inh^{-1} in influent, these are far higher than the 2.1 g d^{-1} 1,000 inh^{-1} mass loads calculated from the work by Castiglioni et al., in Italy (based on the sum of the influent_{AQ} loads of five main classes, 5,049 g d^{-1} , divided by the estimated population (2,400,000) of the contributing WwTWs)(Castiglioni et al., 2018). Though both studies cover a large range of pharmaceuticals, industrial chemicals and personal care products ingredients, Castiglioni's study only has 82 CECs, compared to 138 in this study, though both contain many similar high usage CECs. Furthermore, there are likely to be large differences in prescriptions and industrial contribution between Italy and the UK.

1,082 kg (1,696 kg, including creatinine) is removed from the influent_{AQ} over the course of the study, leaving 72 kg (73 kg including creatinine) in effluent and entering the environment. 51 kg of this is from WwTW E which discharges directly into the estuary, which could not be sampled as part of this study. For the remaining WwTWs the highest contributor, by mass, was WwTW C with 11.6 kg discharged and leads to clear increases in daily river loads both downstream at WwTW C and upstream at WwTW D. The mass discharged by each WwTW generally increases by population equivalents contributing to the WwTWs i.e. WwTW B < WwTW C < WwTW E, however WwTW D, despite having around half the population of WwTW A, shows much higher mass discharge. Normalising the daily load discharge by each WwTW shows the highest population normalised loads are at WwTW D. WwTW A (5 g d^{-1} 1,000 inh^{-1}) < WwTW E (9 g d^{-1} 1,000 inh^{-1}) < WwTW B (12 g d^{-1} 1,000 inh^{-1}) < WwTW C (15 g d^{-1} 1,000 inh^{-1}) < WwTW D (16 g d^{-1} 1,000 inh^{-1} (21 g d^{-1} 1,000 inh^{-1} with creatinine)). Despite this, WwTW D removed the highest mass load per person, 151 g d^{-1} 1,000 inh^{-1} , which is close to WwTW E's removal at 146 g d^{-1} 1,000 inh^{-1} . Based on this TF and SBR show similar removal per person, however, as a proportion of the incoming load WwTW E removed 94.5 %, whereas WwTW D removed 90.4 %. Overall, WwTWs with TF appear to have a lower capacity for removal of CECs than SBR, (WwTWs B and C removed 78.1 % and 88.7 % respectively) whereas WwTW A appears to be the worst with 69.8 % total CEC mass removed. Although, WwTW A showed the lowest contribution with only 0.2 kg over the course

of the study difference between upstream and downstream or $0.7 \text{ g d}^{-1} 1,000 \text{ inh}^{-1}$. The small discharge into a large river at WwTW D, shows only a small difference between upstream and downstream of 0.4 kg over the course of the study or $3 \text{ g d}^{-1} 1,000 \text{ inh}^{-1}$ in the river. WwTW B and C had the highest increase in mass between upstream and downstream at 6.5 kg and 10.2 kg , or 14 and $13 \text{ g d}^{-1} 1,000 \text{ inh}^{-1}$, respectively. Overall, the river upstream of WwTW A contained total mass loads of 1.8 kg , or 287 g d^{-1} , which increased to 25.2 kg , or 3.6 kg d^{-1} downstream of WwTW D (distance between A and D, is approximately 60 km). Throughout the catchment, 10.4 kg d^{-1} was discharged into the environment from the studied WwTWs.

3.3. Impact of effluent discharge to receiving river water

The river upstream of the WwTW A had 50/138 CECs above MQL ranging from 0.02 g d^{-1} (cocaine) to 47.8 g d^{-1} (caffeine), which is due to other smaller WwTWs present upstream, leaching from landfills sites, and possible infiltration from septic tanks, which are often used in more rural areas in the UK. Other classes such as plasticisers, veterinary pharmaceuticals, pesticides, fungicides and herbicides may possibly be present as well, due to surface runoff. Samples from the river downstream of the sites show higher loads overall, but also a different distribution of classes, with anti-diabetics, namely metformin, present at a larger proportion (from first being undetectable upstream of WwTW A, to representing $1,309.6 \pm 135.5 \text{ g d}^{-1}$ downstream of WwTW D). Daily loads ranged from 0.005 g d^{-1} (ketamine, WwTW A) to $1,890.3 \text{ g d}^{-1}$ (metformin, WwTW C, equivalent to $\sim 1,890$ tablets (DrugBank, 2015)) for the 84/138 CECs that were detected downstream of the WwTWs. This trend of increasing load down the river is both expected, although perhaps not to this degree, and concerning.

Figure 4 (and Figure S5-6) show spatial trends of daily cumulative load and shows a steady increase down the river. Similar trends have been seen in Italy with samples which were collected in the River Lambro basin either side of Milan (Castiglioni et al., 2018). WwTW C is clearly the highest contributor to river load, which is not surprising as it has the highest population out of WwTWs A-D. The key classes of importance in river water are anti-diabetics, human indicators, NSAIDs, antihistamines, antibiotics, UV filters and analgesics and metabolites which contribute large portions to the total load with the river. This is interesting

to compare with the distribution of classes within effluent, as analgesics and metabolites appear to contribute far more highly to effluent (21.0 %), however downstream from the discharge point they contribute far less, only 7.3 %. This indicates that once in the environment, they are far less persistent in the aqueous phase than other classes. A similar trend can also be seen for anti-depressants. Whether these compounds are truly degraded or have partitioned to solid phases (e.g. soils and sediments) within this river will need further investigation. However, a spatio-temporal study in the Llobregat showed that psychiatric drugs, among many other pharmaceuticals, were at levels ranging from 4.41 - 18.02 ng g⁻¹ in sediment between the two sampling campaigns and locations. This may be indicative of partitioning to solid phases within the river of this catchment. Sertraline in particular showed high concentration levels in Llobregat with 12.08 ng g⁻¹ in one sampling campaign (Osorio et al., 2016). Furthermore, antibiotics, such as tetracyclines, will pose further concern as they have been shown to preferentially partition to sediment over surface waters (Kim and Carlson, 2007).

Anti-diabetics, metformin specifically, despite high level of removal (78.7 %), still represent a large proportion of effluent load (15.0 kg of 72.6 kg of the estimated total of the campaign, 20.7 % (Figure 3)). It shows that this removal level is insufficient in preventing anti-diabetics from entering the environment, as an increasing trend is observed through the catchment, as seen in Figure 7. A similar situation is seen for the lifestyle chemicals, which represents 38.6 % of the influent_{AQ} load and despite their high removal rates they are at quantifiable levels in the environment and show an increasing trend through the catchment (Figure 7). This is less so for NSAIDs, which are similarly prevalent in influent_{AQ}, at 36.8 % of influent_{AQ} load on average, but show less of an increase through the catchment. Diclofenac shows clear decreases in loads between sites, whether this is degradation or partitioning to solids, is yet to be determined. However, it has been previously found to partition to river sediments downstream of discharge points, along with other NSAIDs, therefore this fate seems likely within this catchment (Duan et al., 2013).

Benzophenone-3, methylparaben and propylparaben are shown to increase between downstream at WwTW B and upstream at WwTW C. For many other CECs, there is a slight increase suggesting the presence of another source of these compounds in the catchment. The increase of these compounds, associated with

personal care products, could be due to much smaller WwTWs contributing to tributaries in the area, however, a similar increase in other CECs would also be expected e.g. carbamazepine, which is not seen. These CECs are usually found in greywater, i.e. from showers and washing. It is currently allowed, although not advised, for greywater from boats to be disposed of directly into the river. It is a practice that may be common in areas outside of marinas where disposal points are few and storage of wastewater onboard is limited and reserved for sewage (Canal and River Trust, 2017). Therefore, the presence of a large number of moorings in this area may contribute to this increase in personal care product ingredients. However, further investigation is required as both locations were not sampled at the same time and the use of grab sampling adds a level of uncertainty.

The river trends of flufenacet and oxadiazon show some small contributions from WwTWs, however the increase between downstream at one site and upstream at the next (particularly between WwTW B and C) supports entry is not primarily via WwTWs but further investigation would be needed to determine the source. Entry of pesticides into environmental surface waters has previously been attributed to diffuse sources such as agricultural application, particularly in proximity to surface waters and further surface runoff during wet weather (Lefrancq et al., 2017; Stuart et al., 2012). Due to the planning of the sampling campaign, rainfall and surface water runoff were at a minimum though this still seems likely to be a source, especially considering the level of agriculture and proximity of farming fields adjacent to the river throughout most of the catchment.

3.4. Presence of micropollutants in digested sludge for land application

An alternative route of entry for anthropogenic micropollutants into the environment is the application of digested sludge (biosolids) onto agricultural land. This area is often overlooked due to the additional analytical requirements to extract micropollutants from solid matrices and the lack of good analytical approaches available (Petrie et al., 2014b). Within the catchment, two WwTW sites had facilities for anaerobic digestion of sludge. WwTWs B and E both receive tankered and piped sludge (primary and secondary) from WwTWs within the catchment in addition to the sludge produced on site.

Digested sludge collected from WwTWs B and E was found to contain 65/96 different CECs (Table S5). This included NSAIDs (1.8 % of the total CEC concentration in digested solids (Figure 5)), antidepressants (10.6 %) and analgesics (1.9 %) which were ubiquitous in all samples studied. Ibuprofen, naproxen and diclofenac were all found in digested sludge, with ibuprofen at the highest concentrations for the class with $200 \pm 42 \text{ ng g}^{-1}$ dry weight (dw) at WwTW B. Although these concentrations are comparable to those previously reported (Guerra et al., 2014; Martín et al., 2012; Radjenović et al., 2009; Sabourin et al., 2012). Of the 12 antidepressants and metabolites studied and quantifiable in sludge, all were detected, including paroxetine and duloxetine which were found in no other samples throughout the catchment. This is attributed to their tendency to sorb to organic matter in wastewater and during treatment, as well as their recalcitrance in biologically mediated processes. Amitriptyline, sertraline and citalopram were present at concentrations $> 400 \text{ ng g}^{-1}$. Morphine was the analgesic found at the highest levels with a mean concentration of $413 \pm 43 \text{ ng g}^{-1}$ at WwTW E. For such compounds, there is limited published data on their occurrence.

Other CECs found at notable concentrations ($>100 \text{ ng g}^{-1}$) were methylparaben, BPA, chloramphenicol, ketoconazole, gemfibrozil, propranolol, carbamazepine and nicotine. Of these micropollutants, BPA was found at the highest levels with mean concentrations of $4,366 \pm 260 \text{ ng g}^{-1}$ (WwTW B) and $37,025 \pm 4,229 \text{ ng g}^{-1}$ (WwTW E) (Table S5). These concentrations are greater than has been observed in previous studies, which have found BPA at concentrations of $\sim 1,000 \text{ ng g}^{-1}$ (Langdon et al., 2014; Samaras et al., 2013) to $14,400 \text{ ng g}^{-1}$ (carbon normalised concentrations) (Kinney et al., 2006). The levels reported here are attributed to the relatively high concentrations observed in receiving wastewater from industrial activities. In this study, BPA contributed 76.1 % to the total concentration in digested solids.

As described by Carballa et al., and Hyland et al., several factors including physicochemical properties of both digested solid and the CECs, as well as the pH, temperature and water content may influence sorption of CECs to the digested solids (Carballa et al., 2008; Hyland et al., 2012). Crucially, the CECs present in digested solids, which have affinity with the aqueous phase, e.g. ibuprofen and naproxen, may not stay partitioned to the solids upon application of digested solids to the environment. These may enter landfill leachates or surface runoff from agricultural applications and may enter the aqueous environment via this route.

Other CECs such as BPA show some recalcitrance in amended soils, possibly due to strong sorption and lack of bioavailability, leading to a lack of degradation as found in a fraction of BPA by Zhang et al., (Zhang et al., 2015).

4. Conclusions

This paper aimed to investigate the changes in micropollutants load throughout a river catchment system in the South-West of the UK, to gain further information on their sources, fate and behaviour. This was achieved by undertaking a comprehensive investigation of an extended list of 142 CECs at five strategic WwTWs representing >75 % of the wastewater from the catchment population. The main conclusions are as follows:

1. Lifestyle, availability of pharmaceuticals without prescription and industry have the biggest effects on the content of influent. Population size and the extent of urbanisation are key drivers of high variability across the catchment, and increased levels of CECs in the environment down the catchment. This is confirmed by normalisation of CEC loads for population, which results in a more even distribution of population normalised CEC loads across the catchment ($154 \pm 12 \text{ mg d}^{-1} \text{ inh}^{-1}$).
2. The analysis of influent_{AQ} and influent_{SPM} is key to determine true levels of CECs entering the works. Furthermore, each phase has a distinct chemical composition and some CECs may be found primarily in one phase or the other. Without analysis of both, a holistic understanding of pollutant fluxes is not possible.
3. Investigating temporal trends can highlight potential instances of incorrect use, incidental release or direct disposal. Although this is evident in both phases, it is particularly clear in the solid phase in this study, e.g. carbamazepine and ketoconazole. Furthermore, the current impact of these sudden, acute, events is currently unknown but may have noticeable effects on wastewater treatment processes or pose an environmental risk.

4. Despite WwTWs not being designed for the removal of CECs, the majority of the studied CECs were removed from the works to the high extent (10.3 kg d⁻¹ remaining in effluent compared to 167.9 kg d⁻¹ in influent). This markedly decreased the potential environmental burden posed by the extent of urbanisation and size of the population within this catchment.
5. Analysis of the river water upstream and downstream of the WwTW discharge point allowed the contribution of each WwTW to the environmental burden to be considered. It also highlights the potential for contribution to the environmental burden from other sources, which may include: septic tanks, sewer overflows, smaller WwTWs, surface runoff and greywater disposal. Furthermore, it showed that many CECs are ubiquitous throughout the catchment, with many increasing in load down the river due to the persistent addition of these compounds to the environment being higher than their degradation rate.
6. Analysis of digested solids has shown high levels of a wide range of CECs present (65/96). These concentrations are significant and considering the potential use of this 'treated' matrix in amended agricultural soils, further consideration should be given to the potential ecological risk of this matrix, which is currently barely understood. Furthermore, the removal trends/treatment efficiency require further study.

Credit author statement

Kathryn Proctor: conceptualisation, writing, sampling, analysis, data collection and interpretation; Bruce Petrie: sampling and analysis; Luigi Lopardo: sampling; Dolores Camacho Muñoz: sampling; Jack Rice:; Ruth Barden, conceptualisation, supervision; Tom Arnot: supervision; Barbara Kasprzyk-Hordern: conceptualisation, writing, supervision.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The support of Wessex Water Services Ltd and the University of Bath EPSRC Impact Acceleration Account (Project number: EP/ K503897/1) is greatly appreciated. Kathryn Proctor would like to acknowledge NERC and Wessex Water for funding her CASE studentship (NE/L009579/1). This work was also supported by the European Union's Seventh Framework Programme for research, technological development and demonstration [Grant agreement 629015, the MC IEF project 'Chiral veterinary medicines in the environment'] and the Leverhulme Trust (Project No RPG-2013-297). All data supporting this study are provided as supporting information accompanying this paper.

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Figure 1 Weekly percentage of total loads in influent_{AQ} of the entire catchment as a pie chart of classes, with chart showing spatial and temporal trends. Note: creatinine is not included. 0.0% shows negligible to no contribution to the total. Numbers in brackets indicate numbers assigned for identification in small figures and table

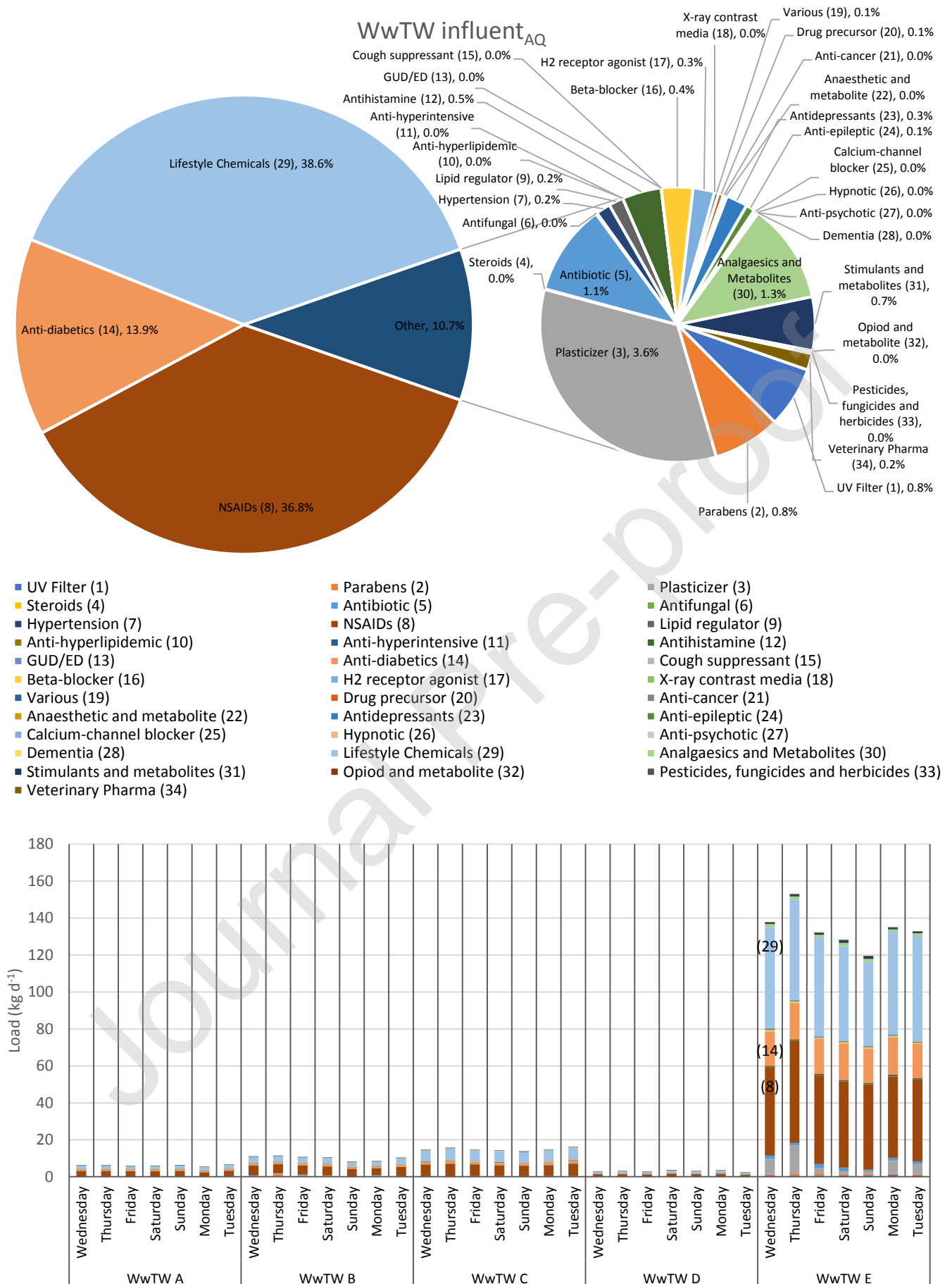
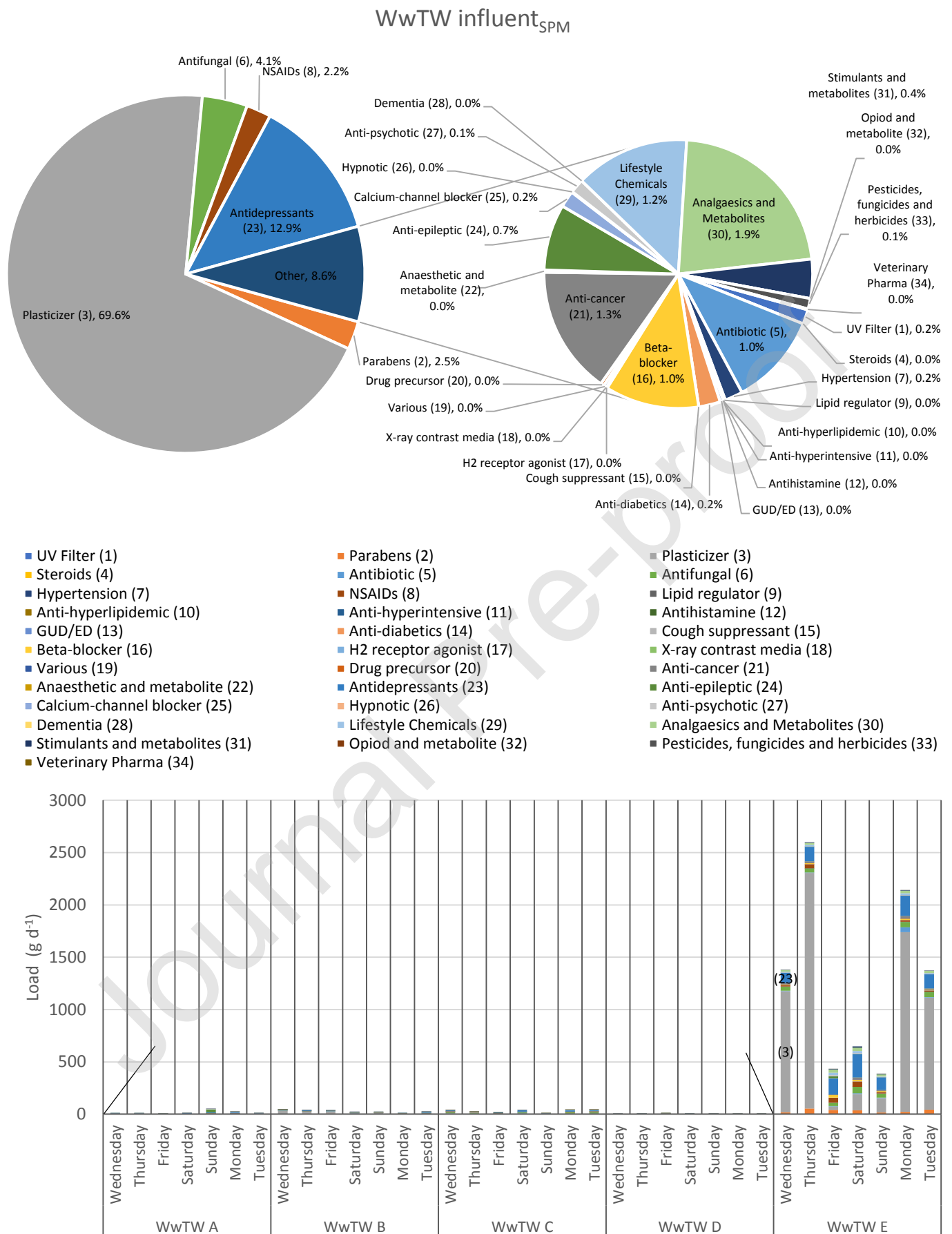


Figure 2 Weekly percentage of total loads in influent_{SPM} of the entire catchment as a pie chart of classes, with chart showing spatial and temporal trends. Note: creatinine is not included. 0.0% shows negligible to no contribution to the total. Numbers in brackets indicate numbers assigned for identification in small figures and table



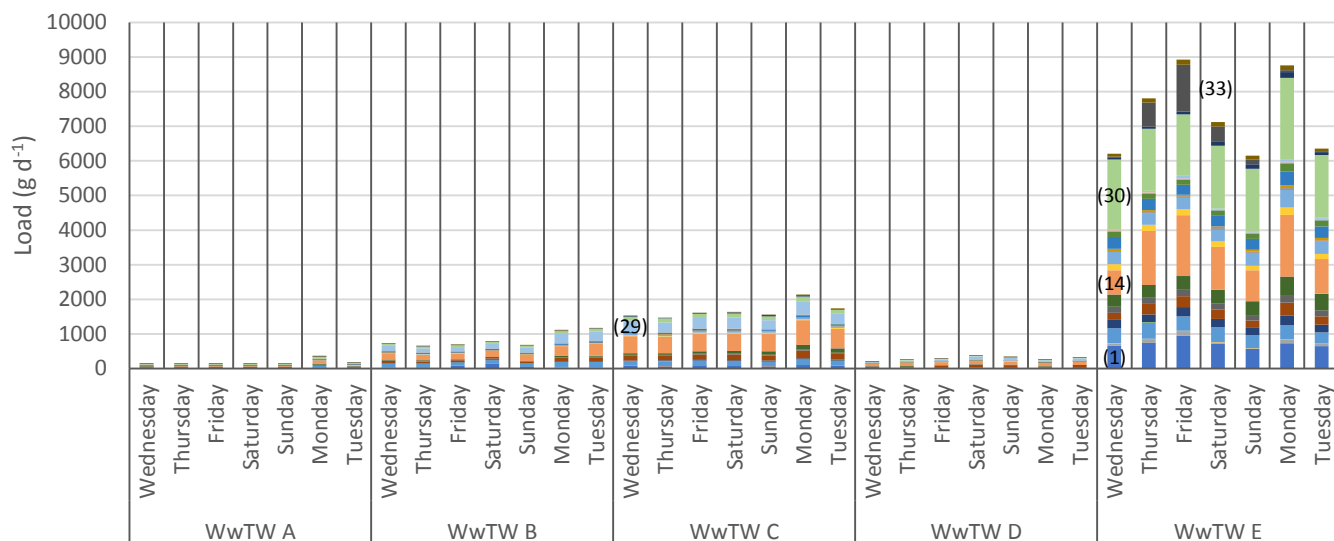
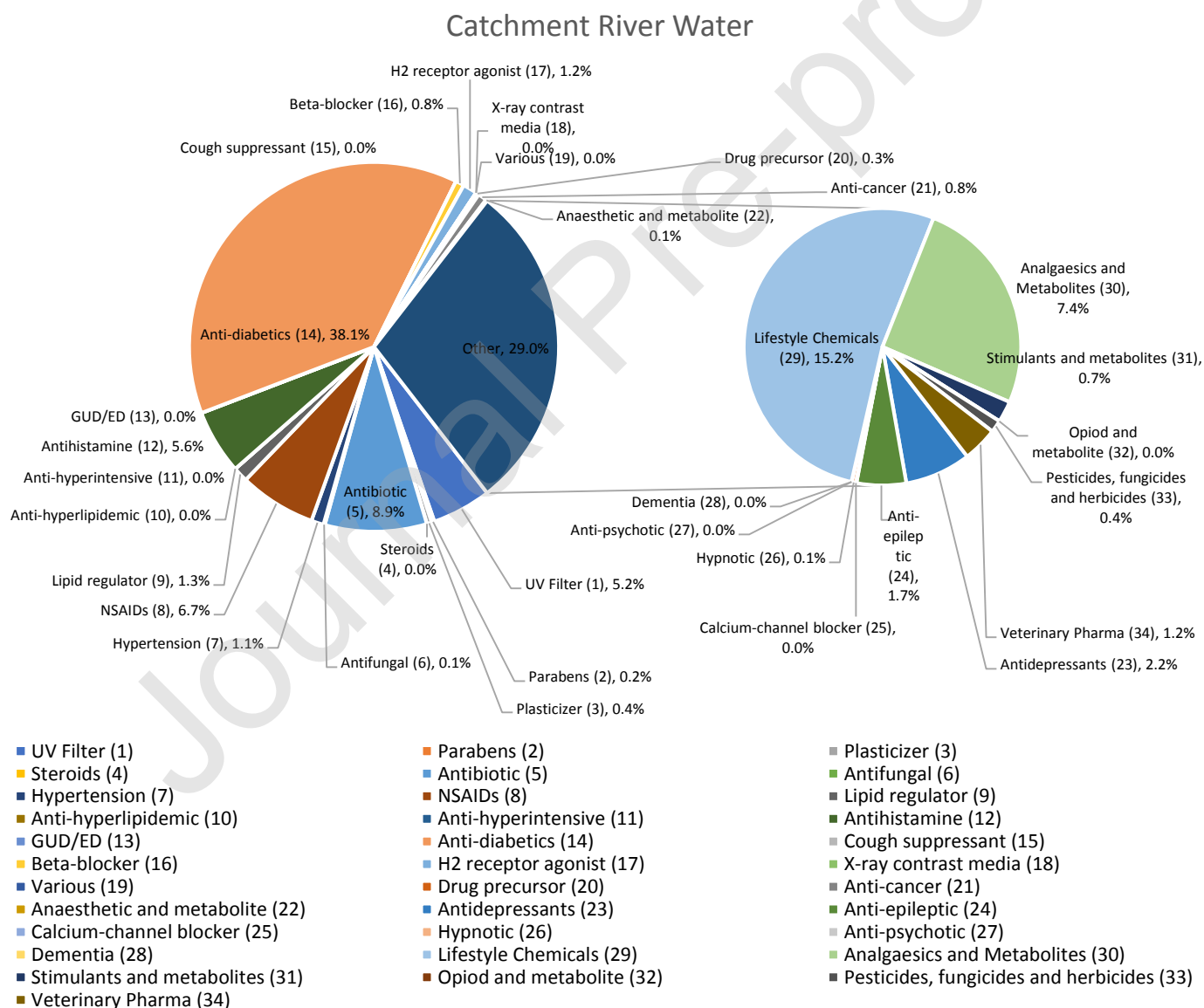


Figure 4 Weekly percentage of total loads in river water of the entire catchment as a pie chart of classes, with chart showing spatial and temporal trends. Note: creatinine is not included. 0.0% shows negligible to no contribution to the total. Numbers in brackets indicate numbers assigned for identification in small figures and table



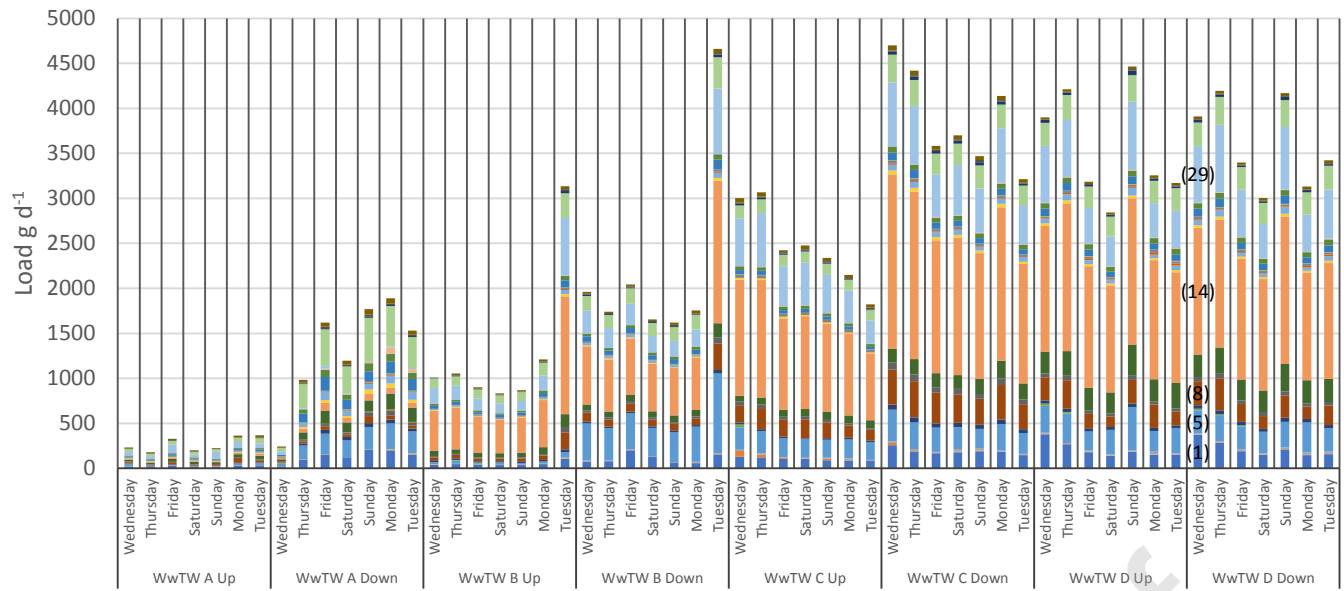
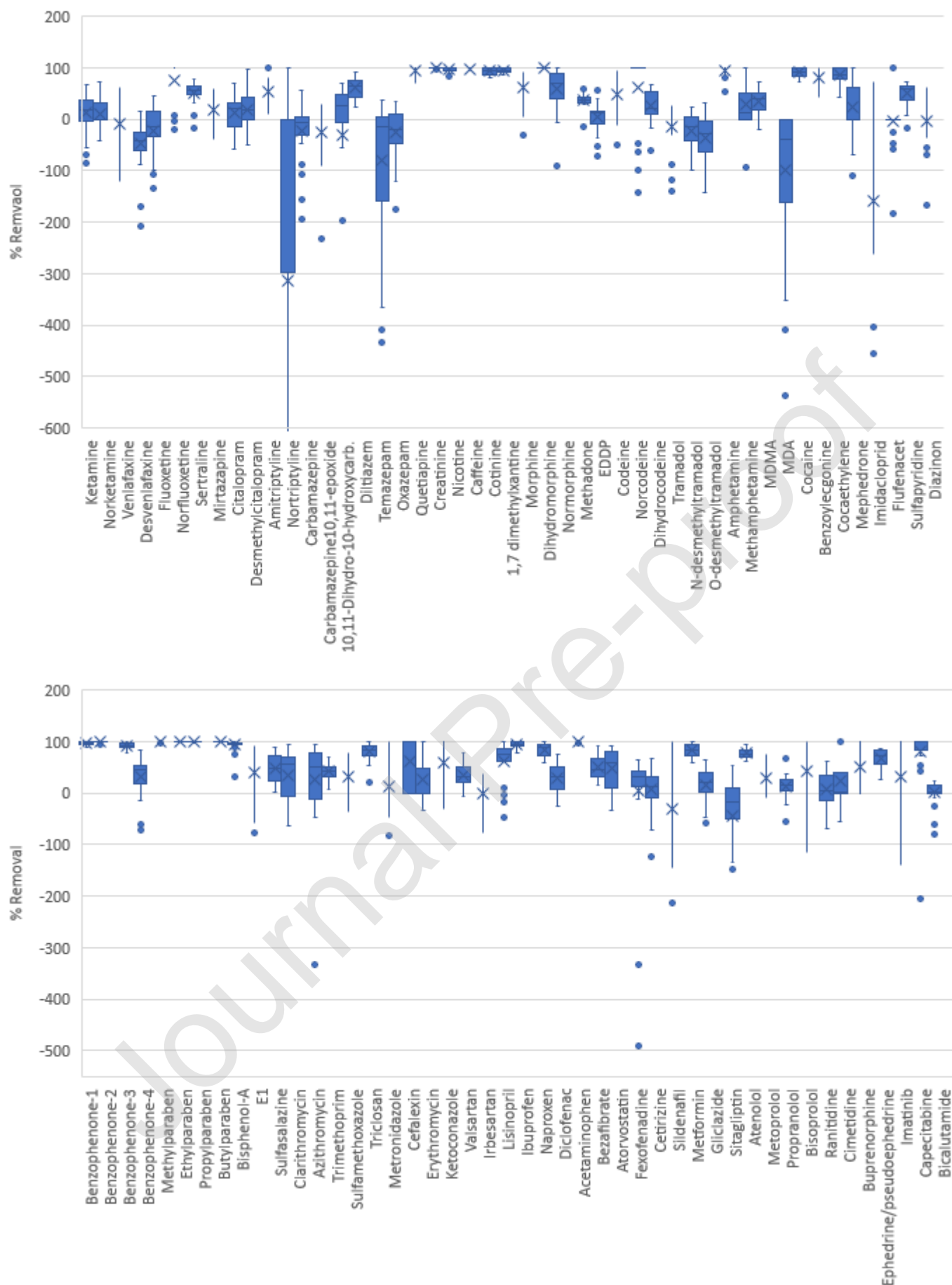
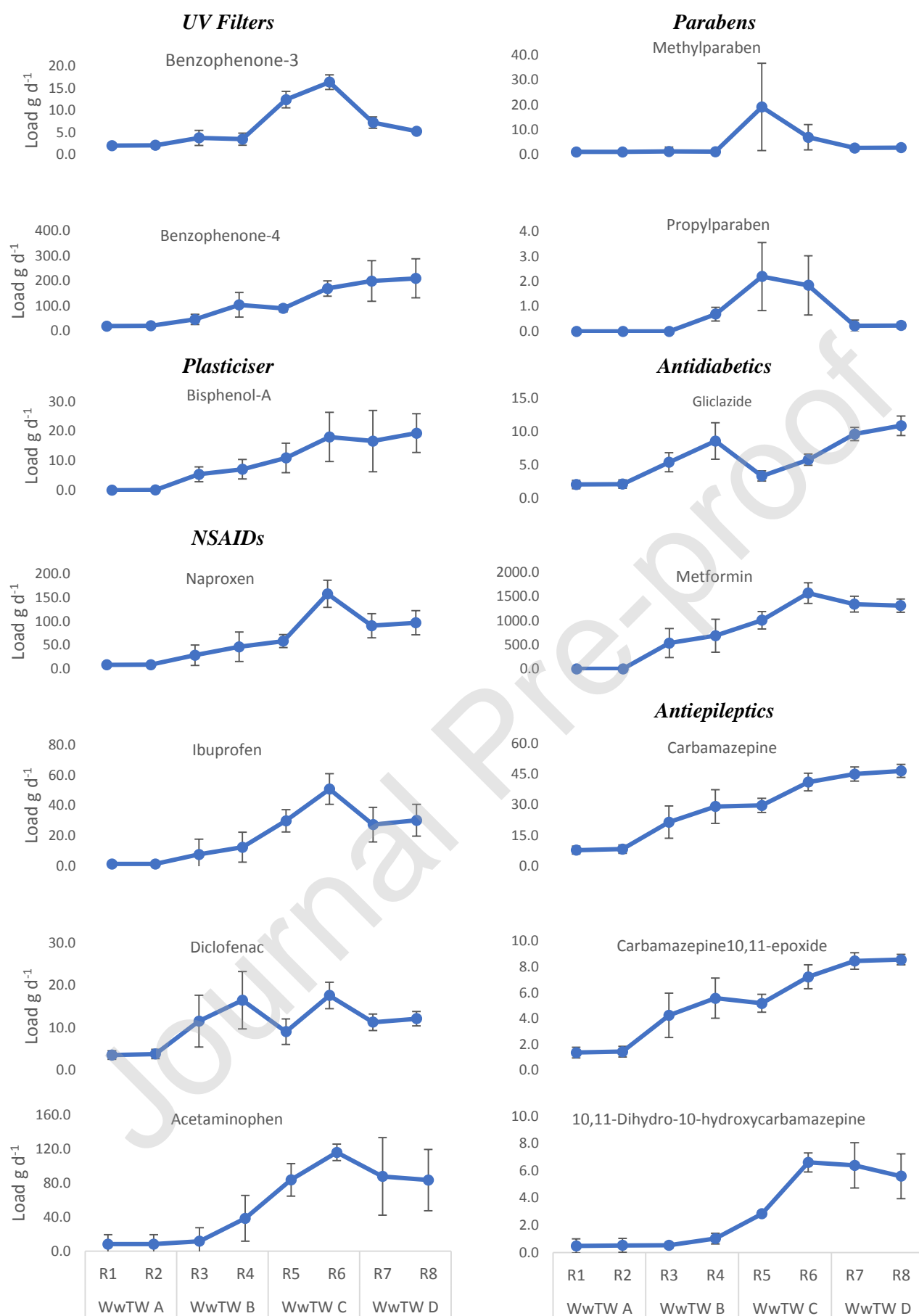


Figure 6 Box plots showing removal of CECs from the liquid phase during WwTW treatment for each site and overall.



*10,11-Dihydro-10-hydroxycarb. = 10,11-Dihydro-10-hydroxy-carbamazepine

Figure 7 Weekly trends for selected compounds. Note: Error bars indicate weekly variation of the sampling site.

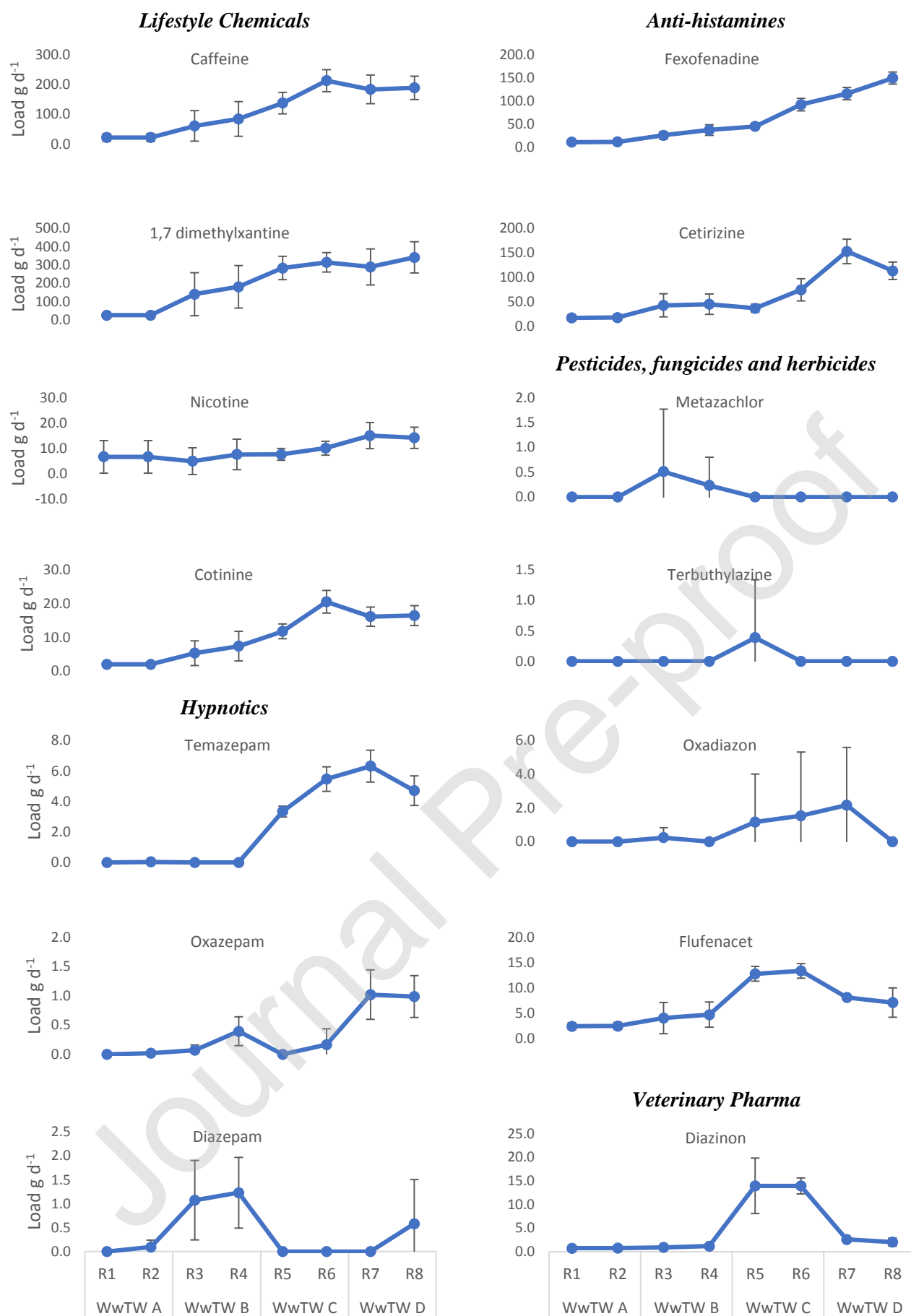
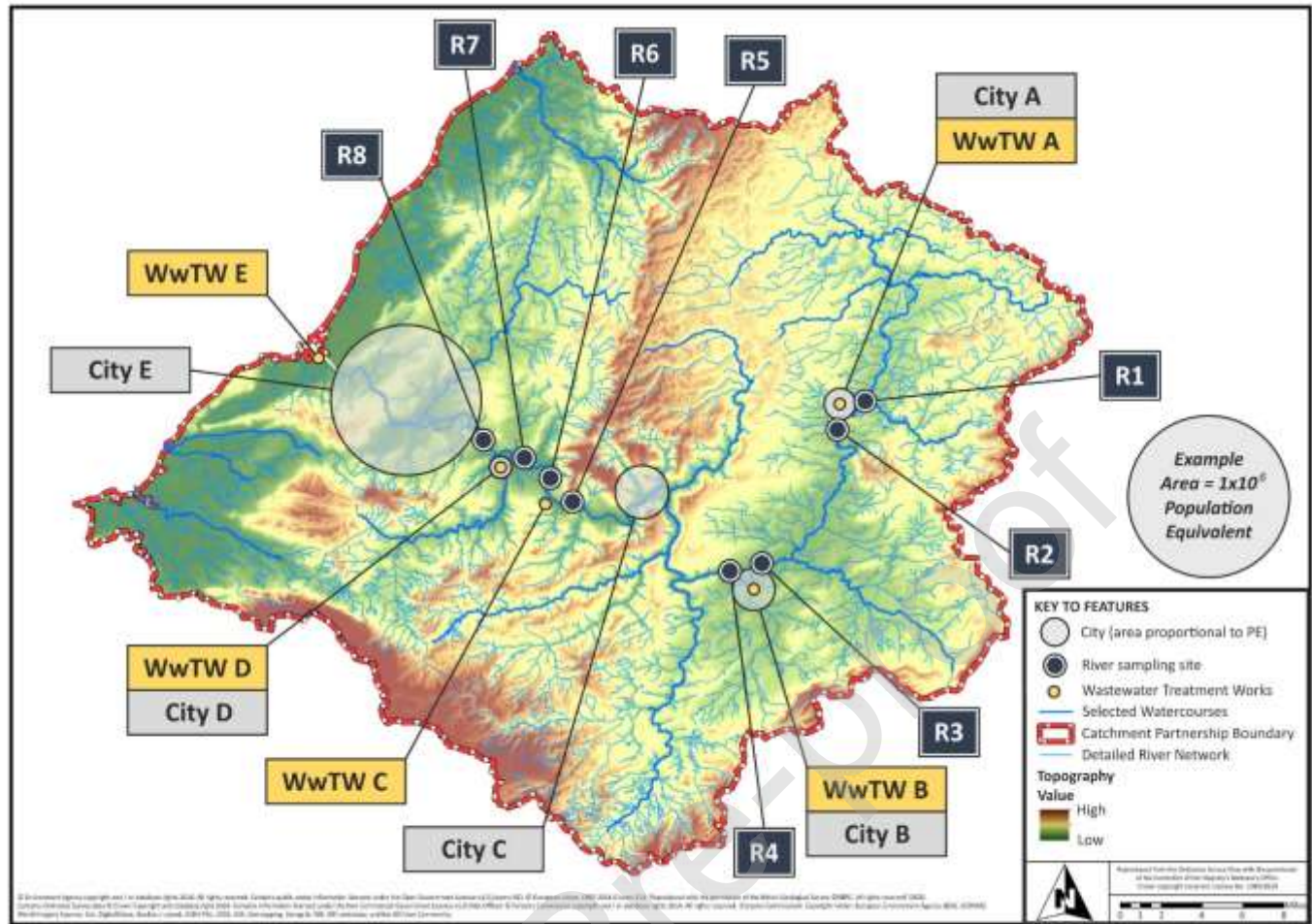


Table 1 Classes of CECs with names of analytes per matrix, total number of analytes in each matrix in first row.

Class	Compound	River	Effluent	Influent	SPM	Dig. Solids	Class	Compound	River	Effluent	Influent	SPM	Dig. Solids
UV Filter	Benzophenone-1	4	4	4	3	3	Anaesthetic and metabolite	Ketamine	2	2	2	2	2
	Benzophenone-2							Norketamine					
	Benzophenone-3						Anti-depressants	Venlafaxine	12	12	13	13	12
	Benzophenone-4							Desvenlafaxine					
Parabens	Methylparaben	4	4	4	4	4		Fluoxetine					
	Ethylparaben							Norfluoxetine					
	Propylparaben							Sertraline					
	Butylparaben							Mirtazapine					
Plasticizer	Bisphenol-A	1	1	1	1	1		Citalopram					
Steroid Estrogens	E1	3	3	3	2	2		Desmethylcitalopram					
	E2							Paroxetine					
	EE2							Duloxetine					
Antibiotics and Antibacterial	Sulfasalazine	19	20	19	7	7		Amitriptyline					
	Clarithromycin							Nortriptyline					
	Azithromycin							Norsertaline					
	Trimethoprim						Anti-epileptic	Carbamazepine	3	3	3	2	2
	Sulfamethoxazole							Carbamazepine10,11-epoxide					
	Triclosan							10,11-Dihydro-10-hydroxycarbamazepine					
	Amoxicillin						Calcium-channel blocker	Diltiazem	2	2	2	1	1
	Metronidazole							Verapamil					
	Sulfadiazine						Hypnotic	Temazepam	3	3	3	2	2
	Cefalexin							Oxazepam					
	Ofloxacin							Diazepam					
	Ciprofloxacin						Anti-psychotic	Quetiapine	2	2	2	2	2
	Tetracycline							Risperidone					
	Danofloxacin						Dementia	Donepezil	2	2	2	2	2
	Oxytetracycline							Memantine					
	Chloramphenicol						Creatinine	Creatinine	5	5	5	2	2
	Penicillin G						Lifestyle Chemicals	Nicotine					
	Penicillin V							Caffeine					
	Erythromycin							Cotinine					
	Prulifloxacin							1,7 dimethylxantine					
Antifungal	Griseofulvin	2	2	2	2	2	Analgesics and Metabolites	Morphine	11	11	11	10	10
	Ketoconazole							Dihydromorphine					
Hypertension	Valsartan	3	3	3	1	1		Normorphine					
	Irbesartan							Metadone					
	Lisinopril							EDDP					
NSAIDs	Ketoprofen	5	5	5	5	5		Codeine					
	Ibuprofen							Norcodeine					
	Naproxen							Dihydrocodeine					
	Diclofenac							Tramadol					
	Acetaminophen							N-desmethyltramadol					
Lipid regulator	Bezafibrate	2	2	2	1	1		O-desmethyltramadol					
	Atorvastatin						Stimulants and metabolites	Amphetamine	10	10	10	8	8
Anti-hyperlipidemic	Gemfibrozil	1	1	1	0	1		Methamphetamine					
Anti-hyperintensive	Candesartan Cilexetil	1	0	0	0	0		MDMA					
Antihistamine	Fexofenadine	2	2	2	0	0		MDA					
	Cetirizine							Cocaine					
GUD/ED	Sildenafil	1	1	1	1	1		Benzoyllecgonine					
	Metformin	3	3	3	1	1		Anhydroecgonine methylester					
Antidiabetics	Gliclazide							Cocaethylene					
	Sitagliptin							Mephedrone					
								MDPV					
Cough suppressant	Pholcodine	1	1	1	1	1	Opioid and metabolite	Heroin	2	2	2	1	1
Beta-blocker	Atenolol	4	4	4	4	4		6-acetylmorphine					
	Metoprolol						Pesticides, fungicides and herbicides	Thiamethoxam	10	10	10	8	7
	Propranolol							Imidacloprid					
	Bisoprolol							Clothianidin					
H2 receptor agonist	Ranitidine	2	2	2	1	1		Metazachlor					
	Cimetidine							Terbutylazine					
X-ray contrast media	Iopromide	1	1	1	1	1		Methiocarb					
Various	Buprenorphine	1	1	1	1	1		Dichlofluanid					
								Flufenacet					
Drug precursor	Ephedrine/pseudoephedrine	2	2	2	2	2		Oxadiazon					
	Norephedrine							Chlorpyrifos					
Anti-cancer	Azathioprine	7	7	7	5	5	Veterinary Pharma	Triallate					
	Methotrexate							Tylosin	5	5	5	1	1
	Ifosfamide							Sulfapyridine					
	Tamoxifen							Sarafloxacin					
	Imatinib							Ceftiofur					
	Capecitabine							Diazinon					
	Bicalutamide												

Table 2 Site information of studied WwTWs and corresponding river locations

Site	Sewer residence time ^a (h)	WwTW secondary process ^b	SRT (d)	HRT ^a (h)	Media type	Configuration	Population served (population equivalents)	Industrial contributions towards population equivalents	Mean flow (m ³ d ⁻¹)	River sampling, distance to discharge point (km)		Effluent-river mass balance ^c (%)
										Upstream	Downstream	
A	<0.5-4	AS	19	46.2	n/a	Carbonaceous & nitrifying	37,714	0.4 %	8,242 ± 3,085	0.5	n/a ^d	n/a ^d
B	<0.5-4	TF	n/a	24.5	Stone	Carbonaceous & nitrifying	68,453	30.0 %	11,202 ± 3,202	0.5	0.5	102
C	<0.5-9	TF	n/a	13.9	Stone – limestone	Carbonaceous & nitrifying	109,543	1.2 %	24,875 ± 2,167	2	2	111
D	<0.5-2	TF	n/a	17.6	Stone – blast furnace slag	Carbonaceous & nitrifying	18,274	0.1 %	2,924 ± 199	1	1	97
E	<1-24	90 % SBR 10 % AS	4 8	10.9 25.8	n/a	Carbonaceous	867,244	23.9 %	153,061 ± 12,245	n/a ^e	n/a	n/a

Key: WwTW, wastewater treatment process; SRT, solids retention time; HRT, hydraulic retention time; p, 'pulses' or toilet flushes; AS, activated sludge; TF, trickling filter; SBR, sequencing batch reactor

^a Under typical summer flows

^b All STWs utilised primary sedimentation dosed with ferric sulfate for phosphorus removal and all processes used conventional sedimentation following secondary treatment except SBRs which decanted following settling *in-situ*

^cMass balances were calculated according to: $Mass\ balance\ (\%) = \frac{Downstream}{Upstream + Effluent} \times 100$ where

Downstream is the load of carbamazepine in river water downstream of the effluent discharge point (g d⁻¹),

Upstream is the load of carbamazepine in river water upstream of the effluent discharge point (g d⁻¹) and

Effluent is the load of carbamazepine in effluent (g d⁻¹)

^dMass balance at site E was > 400 % demonstrating complete mixing of effluent and river water was not achieved at the sampling point due to restricted access to river. Therefore mass loads in river water downstream of the discharge point was calculated by adding effluent loads with river water loads upstream of the discharge point. This assumes complete mixing without any micropollutants losses. Micropollutant concentrations in downstream river water were then estimated using river flow data.

^eEffluent discharged into estuary